Nippon AMR One Health Report (NAOR) 2022

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The AMR One Health Surveillance Committee

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1. Preface

Japan's "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020" was published in April 2016, clearly indicating the implementation of integrated one health surveillance regarding antimicrobial-resistant bacteria that are isolated from humans, animals, food and the environment. This one health surveillance is endorsed as an important strategy for correctly identifying the current status and issues related to AMR, which leads to promoting appropriate national AMR policy. In presenting the results of this surveillance, this report aims to identify the current status of and trends in antimicrobial-resistant bacteria and national antimicrobial amount use (or amount sales) in the areas of human health, animals, agriculture, food and the environment, with the objective of assessing measures to combat antimicrobial-resistant bacteria and clarify challenges in this area.

We hope that this report will serve as a first step to showing the One Health Approach to AMR in Japan and abroad, and that it will also be used by relevant government ministries, agencies, organizations and societies to promote countermeasures and research on AMR.

2. Abbreviations

AMED	Japan Agency for Medical Research and Development
AMU	Antimicrobial Use
AMR	Antimicrobial Resistance
AMRCRC	Antimicrobial Resistance Clinical Reference Center
AUD	Antimicrobial Use Density
BP	Break Point
CDI	*Clostridioides* (*Clostridium*) *difficile* Infection
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem-resistant *Enterobacteriaceae*
DID	Defined Daily Dose per 1000 Inhabitants per Day
DDD(s)	Defined Daily Dose(s)
DOT	Days of Therapy
DOTID	Days of therapy per 1000 Inhabitants per Day
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAMIC	Food and Agricultural Materials Inspection Center
FAO	Food and Agricultural Organization of the United Nations
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Healthcare-associated Infection
ICU	Intensive Care Unit
JANIS	Japan Nosocomial Infections Surveillance
JSAC	Japan Surveillance of Antimicrobial Consumption
J-SIPHE	Japan Surveillance for Infection Prevention and Healthcare Epidemiology
JVARM	Japanese Veterinary Antimicrobial Resistance Monitoring System
MIC	Minimum Inhibitory Concentration
MDRA	Multiagent-resistant *Acinetobacter* spp.
MDRP	Multiagent-resistant *Pseudomonas aeruginosa*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NDB	National Database of Health Insurance Claims and Specific Health Checkups of. Japan
NESID	National Epidemiological Surveillance of Infectious Disease
PID	Number of patients per 1000 Inhabitants per Day
PPCPs	Pharmaceuticals and Personal Products
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
SSI	Surgical Site Infection
WHO	World Health Organization
WOAH	World Organisation for Animal Health
VRE	Vancomycin-resistant *Enterococci*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
DALY(s)	Disability-adjusted life year(s)
PPS	Point Prevalence Survey

3. Classes and Abbreviations of Antimicrobials

Class			Nonproprietary name	Abbreviation*
Beta-lactam antibiotics	Penicillins		Benzylpenicillin (penicillin G)	PCG
			ampicillin	ABPC
			sulbactam/ampicillin	SBT/ABPC
			piperacillin	PIPC
			oxacillin	MPIPC
			tazobactam/piperacillin	TAZ/PIPC
			amoxicillin	AMPC
			clavulanic acid/amoxicillin	CVA/AMPC
	Cephalosporins	1st generation	cefazolin	CEZ
			cephalexin	CEX
		2nd generation	cefotiam	CTM
			cefaclor	CCL
			cefmetazole	CMZ
			cefoxitin	CFX
		3rd generation	cefotaxime	CTX
			ceftazidime	CAZ
			ceftriaxone	CTRX
			sulbactam/cefoperazone	SBT/CPZ
			cefdinir	CFDN
			cefcapene pivoxil	CFPN-PI
			cefditoren pivoxil	CDTR-PI
			cefixime	CFIX
		4th generation	cefepime	CFPM
			cefpirome	CPR
			cefozopran	CZOP
		Cephalosporins combined with beta-lactamase inhibitor	tazobactam/ceftolozane	TAZ/CTLZ
	Cephamycins		cefmetazole	CMZ
			cefoxitin	CFX
	Oxacephems		flomoxef	FMOX
			latamoxef	LMOX
	Monobactams		aztreonam	AZT
	Carbapenems		meropenem	MEPM
			doripenem	DRPM
			biapenem	BIPM
			imipenem/cilastatin	IPM/CS
			panipenem/betamipron	PAPM/BP
			tebipenem pivoxil	TBPM-PI
	Penems		faropenem	FRPM
ST			sulfamethoxazole-trimethoprim	ST
			sulfamonomethoxine	SMMX

Macrolides	erythromycin	EM
	clarithromycin	CAM
	azithromycin	AZM
	tylosin	TS
Ketolides	telithromycin	TEL
Lincomycins	clindamycin	CLDM
	lincomycin	LCM
Streptogramins	quinupristin/dalfopristin	QPR/DPR
	virginiamycin	VGM
Tetracyclines	minocycline	MINO
	tetracycline	TC
	doxycycline	DOXY
	oxytetracycline	OTC
Aminoglycosides	streptomycin	SM
	tobramycin	TOB
	gentamicin	GM
	amikacin	AMK
	arbekacin	ABK
	kanamycin	KM
	spectinomycin	SPCM
	dihydrostreptomycin	DSM
Quinolones (◎fluoroquinolones)	◎ciprofloxacin	CPFX
	◎levofloxacin	LVFX
	◎lascufloxacin	LSFX
	◎pazufloxacin	PZFX
	◎norfloxacin	NFLX
	◎prulifloxacin	PUFX
	◎moxifloxacin	MFLX
	◎garenoxacin	GRNX
	◎sitafloxacin	STFX
	◎ofloxacin	OFLX
	◎enrofloxacin	ERFX
	oxolinic acid	OA
	nalidixic acid	NA
Glycopeptides	vancomycin	VCM
	teicoplanin	TEIC
Oxazolidinones	linezolid	LZD
	tedizolid	TZD
Polypeptides	polymyxin B	PL-B
	colistin	CL
	bacitracin	BC
Lipopeptides	Daptomycin	DAP
Amphenicols	chloramphenicol	CP
	florfenicol	FF

Class	Nonproprietary name	Abbreviation*
Other antibacterial agents	fosfomycin	FOM
	salinomycin	SNM
	bicozamycin	BCM
	trimethoprim	TMP
Antitubercular antibiotics	isoniazid	INH
	ethambutol	EB
	rifampicin (rifampin)	RFP
	pyrazinamide	PZA
	rifabutin	RBT

* Quoted from the Glossary of Antimicrobial Chemotherapy (Japanese Society of Chemotherapy), the Annual Report of the Japanese Society of Antimicrobials for Animals 36 (2014), and the Guidelines for the Use of Antimicrobial Substances in Cooperative Livestock Insurances (2009, Ministry of Agriculture, Forestry and Fisheries)

[Reference] There are multiple relevant terminologies with different definitions. However, in medical practice, the following four terms are often used interchangeably to refer agents that act against bacteria: “antimicrobial agents,” “antibiotics,” “antibiotic agents,” and “antibacterial agents.” In the areas of agriculture and livestock, the expressions "antibacterial agents" and "antimicrobial agents" are commonly used, because these agents are not only used for therapeutic purposes, but also in antibiotic feed additives.

Antimicrobial agents or antimicrobials: Antimicrobial agents, or antimicrobials, are active against microorganisms, which are generally categorized into bacteria, fungi, viruses and parasites. These are the general term for agents to treat and prevent infectious diseases. They contain antibacterial agents, antifungal agents, antiviral agents and antiparasitic agents.

Antibacterial agents: Antimicrobial agents that are active against bacteria.

Antibiotics: chemical substances that inhibit or control the cell activities of microorganisms and other living cells (referred to as antimicrobial activity) and are, strictly speaking, produced by microorganisms.

Antibiotic agents: used as a generic term for anti-microbial agents that act against bacteria.

Reference: the Manual of Antimicrobial Stewardship, 1st edition[1]

In terms of active ingredients (veterinary agents), in terms of effective value (antibiotic feed additives), in terms of active ingredients (agrochemicals), antimicrobial consumption in terms of potency by weight (humans): All these terms refer to active ingredient weight. Quantities in terms of the weight of active ingredients in veterinary agents are calculated from sales data collected from marketing authorization holders for the volume of each agent sold. When doing so, the marketing authorization holders also submit estimates of the percentage of sales for each species of domestic animal, so the estimated volumes sold are calculated for each species based on those estimated percentages. As with the figures for veterinary agents, quantities of antibiotic feed additives in terms of effective value, quantities of agrochemicals in terms of active ingredients, and human antimicrobial consumption in terms of potency by weight refer to active ingredient weight

Indicators of antimicrobial use:

- **AUD:** Mainly used to ascertain usage in medical institutions, AUD is calculated by dividing the total titer of antimicrobials in a specified period by defined daily dose (DDD) as defined by the World Health Organization (WHO), and correcting the result with the total patient-days. The units used for AUD include DDDs per 100 bed-days and DDDs per 1,000 patient-days.

- **DOT :** DOT is a unit mainly used to grasp the usage in medical institutions. It is calculated by correcting the total days of therapy (DOTs) using antimicrobials in a specified period with the total patient-days. The units used for DOT include DOTs per 100 bed-days and DOTs per 1,000 patient-days.

- **DID (DDDs/1,000 inhabitants/day)**: DID is a unit of measurement of use, mainly in a region or country; DID is expressed per 1,000 inhabitants as the total titre over a period of time divided by DDD, with the denominator corrected for the number of inhabitants per day in the region ('inhabitants'). The DID is expressed as a value per 1000 inhabitants, corrected for the number of inhabitants per day.

- **DOTID (DOTs/1,000 inhabitants/day)**: DOTID is a unit that uses claims information to determine usage in a region or country. It is expressed per 1,000 inhabitants as the total number of days of antimicrobial treatment (DOTs) over a period of time in the numerator, with the denominator corrected for the number of inhabitants per day in the region.

- **PID (Number of patients/1,000 inhabitants/day)**: PID is a unit that uses insurance claims information to determine usage in a region or country. It is expressed as a value per 1,000 inhabitants with the total number of people using antimicrobials over a period of time as the numerator and the denominator corrected for the number of inhabitants per day in the region.

[1] https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000193504.pdf

4. Executive Summary

Background:

Japan's "National Action Plan on AMR 2016-2020" positions efforts to ascertain the current status of antimicrobial-resistant bacteria and national antimicrobial use in the areas of human health, animals, food and the environment and trends therein as an important strategy for both evaluating current policy and examining future policy. For global monitoring and reporting, the World Health Organization (WHO) has launched the Global Antimicrobial Resistance Surveillance System (GLASS) for the gathering and sharing of trends in resistant bacteria worldwide. Japan contributes to GLASS by providing our national data. In addition, Japan also submits data as part of our assistance with an initiative by the World Organisation for Animal Health (WOAH), which uses standardized methods for monitoring the volume of antimicrobial use in animals. Accordingly, it is crucial for Japan to update both domestic and overseas stakeholders about the current status and progress of our AMR policy, in order both to reaffirm Japan's position in the global community and to accelerate and advance AMR policy internationally.

Method:

The AMR One Health Surveillance Committee, comprised of experts on AMR in the areas of human health, animals, food and the environment, discussed current surveillance/monitoring systems and reviewed published research on AMR and antimicrobial use. Data on the proportion of antimicrobial resistance among major pathogens in the human medical setting were derived from the Japan Nosocomial Infections Surveillance (JANIS) program organized by the Ministry of Health, Labour and Welfare of Japan. Data on the proportion of antimicrobial resistance among animals and related antimicrobial sales were derived from the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) implemented by the Ministry of Agriculture, Forestry and Fisheries of Japan (MAFF). We obtained data on sales and consumption of antimicrobials for human use from IQVIA Solutions Japan K.K., the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), and Japan Surveillance for Infection Prevention and Health-care Epidemiology (J-SIPHE). Data on the distribution of antimicrobial feed additives were provided by the Food and Agricultural Materials Inspection Center (FAMIC) and the Japan Scientific Feeds Associations (JSFA). Data on the volume of domestic shipments of antimicrobials used as agricultural chemicals was obtained from MAFF, while information on outbreaks of infectious diseases and the implementation of infection control measures was obtained from the National Epidemiological Surveillance of Infectious Diseases (NESID), JANIS and J-SIPHE.

Data on the antimicrobial resistance of microorganisms that are considered pertinent from public health perspective and the public awareness toward AMR, which, however, are not monitored neither by current surveillance nor monitoring systems, were obtained from findings by Health and Labor Sciences Research Groups.

In the animal field, the results of the survey of attitudes of veterinary students at eight universities towards antimicrobial resistance were used.

Results:

In Japan, the carbapenem resistance rate in *Enterobacteriaceae*, particularly *Escherichia coli* and *Klebsiella pneumoniae* has remained below 1% during the observed period, despite its global increase in human isolates. While the resistance rates to third-generation cephalosporins and fluoroquinolones in *E. coli* was on increase in Japan, but decreased slightly in 2021. Although the criteria for carbapenem resistance in *Pseudomonas aeruginosa* were changed in 2014, we believe that the resistance rate is on a decreasing trend. Internationally, the increase in vancomycin resistance among enterococci is a problem. In Japan, although vancomycin (VCM) resistance in *Enterococcus faecium* was 2. 6% in 2022, a relatively low level compared to other countries, it has been increasing in recent years, and widespread hospital outbreaks due to VCM-resistant *E. faecium* were observed in some regions and a record 136 cases were reported to NESID in 2020.

Although the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) had been in an increasing trend again since 2019, started to decrease in 2021. However, it is still high compared to other countries. Clear similarities in the pattern of resistance rates to antimicrobials were observed in serotypes of *Salmonella* spp. isolated from food and from humans, strongly suggesting a link between resistant strains derived from food and from humans.

Antimicrobial use based on human antimicrobial sales in Japan was 9.8 DID in 2021, a 32.8% decrease compared to 2013. Oral antimicrobial agents accounted for 90.9% of total sales, with cephalosporins, fluoroquinolones, and macrolides accounting for the highest shares. The three most frequently used antimicrobial classes in 2021 have also decreased in use by 46.1%, 43.7%, and 47.5%, respectively, compared to 2013. Injectable antimicrobial agents have also decreased by 1.1% compared to 2013. The proportion of "Access" in the AWaRe classification, a guidance for appropriate antimicrobial use recommended by WHO, has gradually increased since 2013, from 11.0% to 23.1% in 2021, while the proportion of "Watch" has decreased from 87.6% to 75.5%.

Surveillance of antimicrobial resistance in animals focuses on food-producing animals (cattle, swine, and chickens), aquatic animals (all farmed fish species), and companion animals (dogs and cats). The resistance rate of *Enterobacteriaceae* to carbapenems, an important antimicrobial class in human medicine, and that of *Enterococcus* spp. to vancomycin, a major problem in human nosocomial infections, were both 0.0%.

Among food-producing animals, while tetracycline resistance in *Escherichia coli* derived from healthy food-

producing animals—an outcome index for the Action Plan—fell from 45.2% in 2014 to 39.9% in 2015, the rate has undergone repeated fluctuations since 2016, and in 2020, it was 45.0%, the same level as in 2019. On the other hand, rates of resistance to third-generation cephalosporins and fluoroquinolones mostly remained below 10% between 2014 and 2020.

Among aquatic animals, resistance rates to lincomycin remained at 61.0% in 2017, 31.5% in 2018, 55.2% in 2019 and 53.8% in 2020 in the causative agent of alpha-hemolytic streptococcosis (*Lactococcus garvieae*) from diseased fish. Resistance rates to both of erythromycin (EM) and oxytetracycline (OTC) remained low at 0.6% in 2020.

Among companion animals, while *Escherichia coli* isolated from diseased dogs and cats demonstrated lower resistance rate to tetracyclines and aminoglycosides than among food-producing animals, resistance rates to the fluoroquinolones and cephalosporins that are critically important antimicrobials for human medicine tended to be higher. *Escherichia coli* isolated from healthy companion animals (dogs and cats) demonstrated lower resistance rate to all antimicrobials than in the case of diseased ones, demonstrating that susceptibility is being broadly maintained. The volume of sales of antimicrobials used for animals (food-producing animals, aquatic animals, and companion animals) was calculated in metric tons (t) of the active ingredients, based on sales reports for antibiotics and synthetic antimicrobials mandated by Article 71-2 of the Regulations for Veterinary Agents (Ordinance of the

Ministry of Agriculture, Forestry and Fisheries No. 107 of 2004). In 2020, tetracyclines represented the largest share of antimicrobial sales, accounting for about 40%. In contrast, third-generation cephalosporins and fluoroquinolones each accounted for less than 1% of the total. The total volume of veterinary antimicrobial sales remained around 800 t, with 842.9 t in 2020, little changed from 841.37 t in 2019. Looking at the figures by class, sales of tetracyclines fell by about 9 t, which was largely due to the decline in use for swine. On the other hand, sulfonamides increased by about 14 t, which was observed in cattle and poultry. Erythromycin for aquatic animals started to decline. In 2020, the estimated use (or sales) of antimicrobials (tonnes: t), based on sales volumes and other data for each sector, were 501.9 t for humans, 626.8 t for livestock, 208.0 t for aquatic animals, 8.1 t for companion animals, 234.8 t for antimicrobial feed additives and 135.9 t for pesticides, totaling 1715.5 t.

Observations:

Antimicrobial use based on sales of oral antimicrobials, including oral cephalosporins, oral macrolides and oral fluoroquinolones in 2021 was found to be lower than in 2013 and, as in 2020, significantly lower than the previous trend. Antimicrobial resistance rates also continued to decline in some species, indicating progress towards achieving the Action Plan's numerical targets. In addition, the resistance rates of third-generation cephalosporins and fluoroquinolones in *Escherichia coli* have decreased slightly.

As the effects of COVID-19 on antimicrobial use and antimicrobial resistance rates are also to be considered, they need to be carefully monitored and their impact assessed in the future. The data in this report demonstrate that further promotion of measures against AMR will be required. There are reports of a correlation between fluoroquinolone usage and the frequency of occurrence of fluoroquinolone- resistant *Escherichia coli*. There are also reports of a connection between the rate of methicillin resistance in *Staphylococcus aureus* and the usage of third-generation cephalosporins, fluoroquinolones, and macrolides. Accordingly, unnecessary use of third-generation cephalosporins, fluoroquinolones, and macrolides must be continuously reduced and the Manual of Antimicrobial Stewardship employed to promote the proper use of antimicrobials, primarily in respect of acute respiratory tract infections. In order to understand the progress, a system has been launched to monitor the use of antimicrobial agents in outpatients in the clinic setting, and its utilization is expected in the future. In promoting the appropriate use of antimicrobials, it is essential that appropriate antimicrobials are available when needed, and it is important to ensure a stable supply of basic antimicrobials. In addition, it is desirable to promote antimicrobial selection and infection control measures based on local conditions by using systems such as J-SIPHE and the AMR One Health Platform. Furthermore, in promoting the appropriate use of antimicrobials, it is necessary to continue education and awareness-raising activities using various methods for the public and healthcare professionals.

Among animals, the resistance rate of *Enterobacteriaceae* resistant to carbapenems, an important antimicrobial class for human medicine, and that of enterococci to vancomycin, a major problem in nosocomial infections in humans, were 0.0% for any livestock species or bacteria. However, rates of resistance to third-generation cephalosporins and fluoroquinolones in *Escherichia coli* isolated from diseased companion animals, surveillance of which began in 2017, were found to be higher than in *Escherichia coli* isolated from food-producing animals. This demonstrates the necessity of continuing and enhancing measures to combat antimicrobial resistance in the field of companion animals through not only via the measures that have been underway for some time in the field of food-producing animals, but also through the widespread circulation of the guide to prudent use in companion animals launched in 2020.

The resistance rates of *E. coli* from healthy food-producing animals to third-generation cephalosporins and fluoroquinolones, an outcome indicator of the Action Plan, have been maintained at a low level and are expected to meet their targets. It is important to continue to educate veterinarians and producers to use these agents with caution as second-line agents. On the other hand, resistance rate to tetracyclines was higher than its target. While

tetracycline sales have been declining since 2018, the resistance rate to them hasn't changed. It is necessary to continue to promote the proper and prudent use of tetracyclines and to monitor trends in its resistance rate.

The existing Action Plan covers the five-year period up to 2020. Although some indices are improving, there are still many that have seen only scant improvement, added to which a number of new issues have emerged, so it is necessary to continue addressing them in coordination with international trends. In the future, industry, academia, and government will work together to promote frameworks for collaboration between the organizations tasked with handling different fields, while also examining the promotion of research that enables cross-cutting evaluation of the risks to humans, animals, and the environment to be conducted.

**Enterobacteriaceae*

Some members of the *Enterobacteriaceae* family have been reclassified and made independent as a new family. In response, it has been advocated to use the term Enterobacterales as synonymous with the old *Enterobacteriaceae*. However, to avoid confusion, in this report, *Enterobacteriaceae* is used to include *Proteus*, *Providencia*, and *Morganella*, which belong to the family *Morganellaceae* family, and *Serratia*, which belongs to the *Yersiniaceae* family.

5. Outcome Indices for the Action Plan

Human-related indices for the Action Plan: proportion (%)[*] of specified antimicrobial-resistant bacteria

	2013	2014	2015	2016	2017	2018	2019	2020	Year 2021	2020 (target value[†])
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, CSF specimens[§]	47.4	47.0	40.5	36.4	29.1	38.3	32.0	33.3	59.5	15% or lower
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, non-CSF specimens[§]	3.2	2.5	2.7	2.1	2.1	2.2	2.2	3.5	3.4	
Proportion of fluoroquinolone-resistant *Escherichia coli*	35.5	36.1	38.0	39.3	40.1	40.9	41.4	41.5	40.4	25% or lower
Proportion of methicillin-resistant *Staphylococcus aureus*	51.1	49.1	48.5	47.7	47.7	47.5	47.7	47.5	46.0	20% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Imipenem)	17.1	19.9	18.8	17.9	16.9	16.2	16.2	15.9	15.8	10% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Meropenem)	10.7	14.4	13.1	12.3	11.4	10.9	10.6	10.5	10.3	10% or lower
Proportion of carbapenem-resistant *Escherichia coli* (Imipenem)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Escherichia coli* (Meropenem)	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Imipenem)	0.3	0.3	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Meropenem)	0.6	0.6	0.6	0.5	0.4	0.5	0.4	0.4	0.4	0.2% or lower (maintain at the same level) [¶]

	2013	2014	2015	2016	2017	2018	2019	2020	Year 2021	2020 (target value[†])
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, CSF specimens[§]	47.4	47.0	40.5	36.4	29.1	38.3	32.0	33.3	59.5	15% or lower
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, non-CSF specimens[§]	3.2	2.5	2.7	2.1	2.1	2.2	2.2	3.5	3.4	
Proportion of fluoroquinolone-resistant *Escherichia coli*	35.5	36.1	38.0	39.3	40.1	40.9	41.4	41.5	40.4	25% or lower
Proportion of methicillin-resistant *Staphylococcus aureus*	51.1	49.1	48.5	47.7	47.7	47.5	47.7	47.5	46.0	20% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Imipenem)	17.1	19.9	18.8	17.9	16.9	16.2	16.2	15.9	15.8	10% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Meropenem)	10.7	14.4	13.1	12.3	11.4	10.9	10.6	10.5	10.3	10% or lower
Proportion of carbapenem-resistant *Escherichia coli* (Imipenem)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Escherichia coli* (Meropenem)	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Imipenem)	0.3	0.3	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Meropenem)	0.6	0.6	0.6	0.5	0.4	0.5	0.4	0.4	0.4	0.2% or lower (maintain at the same level) [¶]

CSF, cerebrospinal fluid

* Prepared based on JANIS data. Data were provided every two years from 2013, but annual data have been provided since 2017.

† Target values were quoted from the National Action Plan on AMR.[1]

§ The proportion of penicillin-non-susceptible *Streptococcus pneumoniae* in 2014, as indicated in the Action Plan, is based on the CLSI (2007) Criteria where those with penicillin MIC of 0.125 μg/mL or higher are considered resistant. The CLSI Criteria were revised in 2008, applying different standards to CSF and non-CSF specimens. Based on this revision, JANIS has divided data into CSF and non-CSF specimens since 2015. The number of specimens was around 100 (42 in 2021), therefore assessment of the resistance rate should be done with caution.

¶ The National Action Plan on AMR [1] indicates that the respective proportion of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* were at 0.1% and 0.2% in 2014, and the proportions should be maintained at the same level in 2020.

Human-related indices for the Action Plan: use of antimicrobials (DID) (based on volume of sales)

	2013[†]	2021	Change from 2013	2020 (target value*)
All antimicrobials	14.52	9.77	32.7%↓	33%↓
Oral cephalosporins	3.91	2.11	46.1%↓	50%↓
Oral fluoroquinolones	2.83	1.48	43.7%↓	50%↓
Oral macrolides	4.83	2.72	47.5%↓	50%↓
Intravenous antimicrobials	0.90	0.89	1.1%↓	20%↓

DID: Defined daily dose per 1,000 inhabitants per day

* Target values were quoted from [1].

[†] Prepared from [2] and [3].

Animal-related indices for the Action Plan: proportion (%) of specified antimicrobial-resistant bacteria

		2014*	2015*	2016	2017	2018	2019	2020	2020 (target value**)
Proportion of tetracycline-resistant *Escherichia coli*	(farms)	45.2	39.9						33% or lower
	(Animal slaughterhouses)		39.8	47.6	40.8	43.6	44.3	45.0	
Proportion of third-generation cephalosporin-resistant *Escherichia coli*	(farms)	1.5	0.9						The same level as in other G7 nations***
	(Animal slaughterhouses)		0.7	2.4	2.1	1.1	2.1	1.4	
Proportion of fluoroquinolone-resistant *Escherichia coli*	(farms)	4.7	3.8						The same level as in other G7 nations
	(Animal slaughterhouses)		2.7	5.0	4.0	4.7	5.1	5.2	

* Prepared from [4] with partial modification. JVARM "Results of Monitoring of Antimicrobial Resistant Bacteria Isolated from Food-producing Animals on Farms"

** Target values were quoted from [1].

***See References [5] and [6].

References

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2. Muraki Y, *et al.* "Japanese antimicrobial consumption surveillance: first report on oral and parenteral antimicrobial consumption in Japan (2009–2013)" J Glob Antimicrob Resist. 2016 Aug 6;7:19-23.
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6. Current Status of Antimicrobial-resistant Bacteria in Japan

(1) Humans

1) Gram-negative bacteria

Source: JANIS

As for the recent status of gram-negative bacteria, despite recent global increase of carbapenem (imipenem (IPM) and meropenem (MEPM))-resistant *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella pneumoniae*, the proportion of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* in Japan remained low at less than 1%, as in Tables 1 and 2. However, the rate of resistance against third-generation cephalosporins such as cefotaxime (CTX) and fluoroquinolones such as levofloxacin (LVFX) among *Escherichia coli* continues to increase but showed a slight decrease for the first time between 2020 and 2021. The rise in the rate of resistance to third-generation cephalosporins would appear to reflect the increase in bacteria with ESBL genes. As such, there appears to be a particular need for measures targeted at the rise of these resistant bacteria. It is too early to determine whether the observed decrease in the resistance rate of *E. coli* to third-generation cephalosporins is transient or the result of a genuine decline, and it is necessary to continue to monitor future trends.

The proportion of carbapenem-resistant *Enterobacter cloacae* (Table 3) and *Klebsiella (Enterobacter) aerogenes* (Table 4) remained between around 1% and 2%; and the proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Table 5) and *Acinetobacter* spp. (Table 6) remained at a level equivalent to or even lower than in other countries. In particular, the proportion of carbapenem-resistant *Acinetobacter* spp. remained low between around 1% and 3%.

i. *Escherichia coli*

Table 1. Resistance rates (%) of *Escherichia coli*

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
ABPC	32	32	47.6 (116,097)	49.1 (133,330)	49.4 (150,867)	49.2 (170,597)	50.5 (257,065)	51.2 (288,052)	51.7 (307,143)	52.2 (325,553)	52.6 (336,351)	51.9 (337,433)	50.4 (340,248)
PIPC	128	128	40.1 (119,843)	41.6 (136,978)	42.5 (155,626)	42.5 (175,763)	44.1 (270,452)	44.9 (305,604)	45.2 (327,773)	46.0 (342,066)	46.4 (343,183)	45.6 (339,444)	44.0 (338,450)
TAZ/PIPC	4/128	4/128	-	-	2.2 (51,286)	1.7 (89,442)	1.7 (179,722)	1.8 (218,008)	1.7 (241,519)	1.7 (263,131)	3.2 (285,685)	2.8 (290,567)	2.6 (303,907)
CEZ*	32	8	24.4 (122,803)	26.2 (141,560)	26.9 (161,397)	33.3 (183,542)	35.8 (268,898)	36.8 (303,608)	37.3 (324,109)	38.7 (347,491)	39.0 (361,167)	38.7 (360,415)	37.4 (363,330)
CMZ	64	64	-	-	-	1.0 (163,342)	0.9 (260,844)	1.0 (300,089)	0.9 (325,296)	0.9 (348,832)	0.9 (365,259)	0.8 (372,259)	0.8 (376,435)
CTX*	64	4	14.8 (99,543)	16.6 (113,354)	17.8 (124,473)	23.3 (140,186)	24.5 (209,404)	26.0 (230,911)	26.8 (241,843)	27.5 (251,068)	28.3 (257,856)	28.3 (257,134)	26.8 (251,869)
CAZ*	32	16	5.2 (123,606)	5.2 (142,440)	5.5 (161,163)	9.5 (183,970)	10.8 (275,671)	11.6 (310,281)	12.0 (330,029)	12.4 (352,819)	14.0 (367,538)	13.9 (369,898)	13.0 (372,255)
CFPM	32	32	-	-	10.9 (81,456)	12.8 (129,606)	15.0 (236,705)	15.8 (273,587)	16.1 (296,143)	16.7 (321,745)	18.1 (337,526)	17.5 (341,664)	16.8 (344,555)
AZT*	32	16	8.5 (97,906)	9.4 (111,930)	10.2 (126,777)	16.1 (143,046)	17.6 (216,494)	18.4 (239,952)	18.7 (258,193)	19.3 (273,064)	21.0 (283,965)	20.4 (284,169)	19.2 (286,755)
IPM*	16	4	0.1 (113,820)	0.1 (128,289)	0.1 (146,007)	0.1 (163,181)	0.1 (251,050)	0.1 (284,316)	0.1 (304,633)	0.1 (321,043)	0.1 (328,665)	0.1 (328,031)	0.1 (330,003)
MEPM*	16	4	-	-	0.1 (95,180)	0.2 (144,913)	0.2 (269,893)	0.2 (317,987)	0.1 (340,687)	0.1 (365,600)	0.1 (379,637)	0.1 (383,513)	0.1 (387,094)
AMK	64	64	0.2 (123,464)	0.2 (141,114)	0.2 (161,406)	0.2 (184,788)	0.1 (281,641)	0.1 (317,913)	0.1 (339,871)	0.1 (362,591)	0.1 (374,518)	0.1 (378,104)	0.1 (380,774)
LVFX	8	8	31.4 (117,292)	34.3 (136,253)	35.5 (155,998)	36.1 (178,497)	38.0 (274,687)	39.3 (310,705)	40.1 (336,310)	40.9 (360,329)	41.4 (374,719)	41.5 (379,538)	40.4 (381,447)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility. Data for ST were not calculated.

-: Not under surveillance

* CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012) (M100-S22) Criteria was applied to determine BP after 2014.

ii. *Klebsiella pneumoniae*

Table 2. Resistance rates (%) of *Klebsiella pneumoniae*

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
ABPC	32	32	75.9 (65,338)	76.9 (73,078)	77.8 (80,030)	76.3 (90,220)	76.9 (131,700)	76.3 (147,500)	77.4 (152,477)	79.4 (158,654)	80.1 (159,790)	79.7 (157,459)	77.7 (160,188)
PIPC	128	128	19.7 (67,548)	20.1 (74,878)	24.3 (82,608)	21.9 (91,761)	21.1 (136,347)	21.8 (154,260)	21.8 (161,254)	22.9 (165,430)	24.5 (161,590)	25.1 (156,799)	26.7 (158,472)
TAZ/PIPC	4/128	4/128	-	-	2.2 (27,279)	2.0 (46,941)	2.0 (91,503)	2.2 (110,189)	2.2 (118,796)	2.6 (127,778)	3.1 (135,732)	3.2 (136,696)	3.6 (145,033)
CEZ*	32	8	8.8 (68,481)	9.0 (76,860)	9.1 (85,320)	11.7 (94,875)	12.1 (135,486)	13.1 (152,973)	13.4 (157,849)	14.3 (166,906)	15.2 (170,001)	16.5 (166,842)	18.2 (170,103)
CMZ	64	64	-	-	-	1.9 (85,749)	1.9 (132,163)	1.7 (152,086)	1.5 (159,375)	1.6 (168,787)	1.5 (172,912)	1.5 (173,615)	1.5 (177,579)
CTX*	64	4	5.2 (56,236)	5.4 (62,242)-	5.1 (66,654)	8.6 (73,574)	8.0 (107,409)	8.9 (118,057)	8.9 (119,672)	9.4 (122,459)	9.7 (122,241)	11.0 (119,269)	11.7 (117,676)
CAZ*	32	16	3.4 (68,916)	2.9 (76,961)	2.7 (84,761)	3.8 (94,878)	4.0 (138,191)	4.6 (155,293)	5.0 (160,619)	5.7 (169,097)	6.9 (173,031)	8.6 (171,425)	9.5 (174,262)
CFPM	32	32	-	-	3.0 (41,143)	3.5 (66,399)	4.0 (119,563)	4.8 (138,737)	5.1 (145,745)	5.8 (156,485)	6.8 (160,502)	7.7 (160,138)	8.5 (163,139)
AZT*	32	16	4.1 (54,680)	3.7 (60,606)	3.5 (67,253)	5.1 (75,340)	5.3 (110,259)	5.9 (122,600)	6.2 (127,491)	6.7 (133,009)	8.0 (135,631)	9.1 (133,016)	10.2 (134,988)
IPM*	16	4	0.2 (63,825)	0.2 (70,284)	0.1 (77,193)	0.3 (85,253)	0.3 (126,997)	0.2 (143,813)	0.2 (149,546)	0.3 (154,879)	0.2 (155,242)	0.2 (151,882)	0.2 (154,691)
MEPM*	16	4	-	-	0.2 (48,190)	0.6 (73,903)	0.6 (135,930)	0.5 (159.623)	0.4 (166,298)	0.5 (175,408)	0.4 (179,042)	0.4 (178,240)	0.4 (182,018)
AMK	64	64	0.3 (68,995)	0.2 (76,293)	0.2 (84,916)	0.1 (95,643)	0.1 (141,710)	0.1 (159,871)	0.1 (166.081)	0.1 (174,259)	0.1 (176,609)	0.1 (175,742)	0.1 (179,422)
LVFX	8	8	2.7 (66,466)	2.4 (74,718)	2.5 (83,063)	2.4 (92,993)	2.6 (138,428)	2.7 (156,249)	2.8 (163,688)	3.1 (172,010)	3.4 (175,799)	4.2 (175,200)	4.6 (178,138)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility. Not under surveillance

* CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012) (M100-S22) Criteria was applied to determine BP after 2014.

iii. *Enterobacter* spp.

Table 3. Resistance rates (%) of *Enterobacter cloacae*

	BP (-2013)	BP (2014-)	2013	2014	2015	2016	2017	2018	2019	2020	2021
ABPC	32	32	80.9 (35,849)	79.0 (39,344)	80.2 (55,960)	79.3 (61,667)	79.8 (61,970)	81.2 (64,820)	81.3 (64,723)	81.4 (62,954)	80.4 (62,121)
PIPC	128	128	20.6 (36,988)	20.0 (39,636)	19.8 (58,039)	20.1 (63,580)	20.8 (64,217)	21.2 (66,020)	21.7 (62,798)	21.6 (60,369)	21.3 (58,758)
TAZ/PIPC	4/128	4/128	10.3 (11,895)	8.6 (21,091)	8.9 (40,315)	8.9 (47,390)	9.4 (48,775)	9.8 (52,186)	10.5 (54,305)	10.3 (54,675)	10.1 (56,350)
CEZ*	32	8	97.2 (37,359)	98.2 (41,422)	98.3 (58,637)	98.3 (64,634)	98.3 (64,693)	98.3 (68,017)	98.2 (68,074)	98.2 (67,036)	98.2 (66,201)
CMZ**	-	64	-	83.4 (37,492)	85.4 (56,647)	85.5 (63,331)	86.1 (64,158)	88.0 (68,013)	87.4 (68,727)	88.1 (68,183)	87.9 (67,430)
CTX*	64	4	19.2 (30,106)	31.1 (32,718)	31.6 (46,727)	31.2 (50,311)	32.4 (50,022)	32.9 (51,470)	33.7 (50,606)	34.0 (49,402)	34.1 (47,591)
CAZ*	32	16	20.6 (37,202)	24.7 (41,456)	25.0 (59,533)	24.9 (65,317)	25.8 (65,027)	26.3 (68,737)	26.8 (69,265)	27.4 (67,922)	27.7 (67,174)
CFPM	32	32	4.2 (17,900)	4.2 (29,836)	4.2 (52,218)	4.0 (58,298)	4.0 (59,398)	3.9 (64,337)	4.0 (65,211)	3.7 (65,110)	3.5 (64,286)
AZT*	32	16	16.8 (29,460)	23.8 (33,551)	24.0 (48,570)	23.9 (52,951)	24.3 (53,374)	24.9 (55,988)	26.1 (56,211)	26.3 (55,380)	26.5 (54,810)
IPM*	16	4	0.4 (34,403)	1.6 (37,396)	1.3 (54,926)	1.2 (60,602)	1.1 (60,689)	1.1 (63,611)	1.2 (61,918)	1.0 (61,234)	0.9 (59,721)
MEPM*	16	4	0.6 (21,164)	1.3 (32,589)	1.4 (59,009)	1.2 (67,250)	1.1 (67,392)	1.1 (71,119)	0.9 (71,548)	1.0 (70,910)	0.8 (70,077)
AMK	64	64	0.4 (37,947)	0.2 (42,005)	0.2 (61,086)	0.1 (67,133)	0.1 (67,125)	0.1 (70,659)	0.1 (70,392)	0.1 (69,812)	0.1 (68,955)
LVFX	8	8	4.2 (37,274)	3.5 (40,942)	3.7 (59,393)	3.4 (65,161)	3.5 (65,690)	3.2 (69,392)	3.1 (70,034)	2.9 (69,816)	2.6 (68,752)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

-: Not under surveillance

* CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012) (M100-S22) Criteria was applied to determine BP after 2014.

Table 4. Resistance rates (%) of *Klebsiella* (*Enterobacter*)* *aerogenes*

	BP (-2013)	BP (2014-)	2013	2014	2015	2016	2017	2018	2019	2020	2021
ABPC	32	32	76.5 (17,362)	77.1 (18,385)	78.9 (26,680)	77.9 (29,228)	79.1 (30,844)	80.3 (32,746)	80.5 (33,621)	80.8 (33,862)	79.6 (35,315)
PIPC	128	128	14.5 (18,029)	14.5 (18,550)	14.2 (27,189)	15.8 (29,852)	17.1 (31,802)	17.4 (33,048)	18.9 (32,497)	18.6 (32,139)	17.5 (32,962)
TAZ/PIPC	4/128	4/128	6.3 (5,568)	4.9 (9,568)	4.8 (18,731)	4.8 (21,767)	5.7 (24,082)	6.9 (26,272)	6.9 (28,085)	7.2 (29,124)	7.0 (30,954)
CEZ**	32	8	90.8 (17,945)	94.0 (19,173)	93.7 (27,526)	94.2 (30,088)	94.5 (31,800)	95.0 (33,996)	94.7 (35,183)	95.1 (35,448)	95.0 (36,851)
CMZ	64	64	-	84.8 (17,587)	86.8 (26,739)	87.1 (29,681)	88.0 (31,915)	89.1 (34,051)	89.5 (35,408)	89.9 (36,068)	90.0 (37,881)
CTX**	64	4	5.2 (14,452)	28.3 (15,173)	30.7 (21,985)	31.1 (23,572)	32.9 (24,195)	33.4 (25,493)	34.2 (26,271)	35.4 (26,655)	35.2 (27,111)
CAZ**	32	16	17.3 (17,992)	24.3 (19,439)	25.2 (27,886)	25.7 (30,388)	26.7 (32,030)	27.8 (34,142)	28.5 (35,487)	29.6 (35,985)	29.7 (37,638)
CFPM	32	32	1.0 (8,909)	1.2 (13,499)	1.1 (24,302)	1.1 (27,146)	1.3 (29.464)	1.4 (32,216)	1.5 (33,583)	1.4 (34,454)	1.5 (36,047)
AZT**	32	16	7.5 (14,639)	15.8 (15,846)	17.5 (23,225)	17.5 (25,023)	18.0 (26,772)	19.2 (28,281)	20.2 (29,397)	20.8 (30,056)	20.4 (31,103)
IPM**	16	4	0.4 (16,881)	1.7 (17,463)	1.9 (25,690)	1.9 (28,307)	1.9 (29,869)	2.6 (31,288)	2.3 (31,645)	2.2 (32,050)	1.7 (33,173)
MEPM**	16	4	0.2 (10,249)	0.9 (15,003)	0.8 (27,560)	0.8 (31,311)	0.8 (33,150)	0.8 (35,448)	0.8 (36,550)	0.9 (37,291)	0.9 (38,989)
AMK	64	64	0.2 (18,369)	0.2 (19,492)	0.1 (28,627)	0.1 (31,338)	0.1 (33,074)	0.1 (35,214)	0.1 (36,204)	0.05 (36,866)	0.05 (38,542)
LVFX	8	8	1.1 (18,111)	1.0 (19,068)	0.9 (28,012)	1.0 (30,451)	0.9 (32,503)	0.9 (34,383)	0.9 (35,735)	0.9 (36.768)	1.0 (38.092)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

-: Not under surveillance

**Enterobacter aerogenes* has been renamed *Klebsiella aerogenes* (Int. J. Syst. Evol. Microbiol. 67, 502-504, 2017).

** CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012) (M100-S22) Criteria was applied to determine BP after 2014.

iv. *Pseudomonas aeruginosa*

Table 5. Resistance rates (%) of *Pseudomonas aeruginosa*

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PIPC	128	128	12.1 (114,950)	11.9 (118,032)	11.4 (122,581)	10.8 (125,242)	10.5 (181,977)	10.5 (201,764)	10.3 (205,165)	10.0 (206,858)	10.3 (214,513)	10.0 (211,455)	9.8 (214,729)
TAZ/ PIPC	4/128	4/128	-	-	9.0 (68,686)	8.8 (79,574)	8.8 (132,769)	8.4 (155,724)	8.3 (165,402)	8.1 (172,748)	8.4 (185,720)	7.8 (185,847)	7.8 (191,294)
CAZ	32	32	11.3 (116,596)	10.9 (120,473)	10.2 (124,864)	9.5 (126,718)	8.6 (180,479)	8.7 (199,597)	8.6 (202,025)	8.4 (203,554)	8.7 (210,892)	8.6 (207,738)	8.7 (211,983)
AZT	32	32	16.3 (96,435)	16.7 (100,964)	16.5 (105,681)	14.5 (107,167)	14.0 (146,841)	13.8 (158,737)	13.7 (162,952)	13.1 (162,365)	13.3 (167,331)	13.6 (164,518)	13.4 (166,971)
CFPM	32	32	9.7 (91,769)	8.9 (99,730)	8.0 (106,291)	7.5 (113,268)	6.6 (166,096)	6.5 (185,283)	6.3 (191,502)	6.0 (194,385)	5.9 (200,818)	5.7 (198,849)	5.5 (202,904)
IPM*	16	8	19.8 (112,596)	18.5 (116,193)	17.1 (119,979)	19.9 (119,323)	18.8 (168,471)	17.9 (186,380)	16.9 (188,981)	16.2 (188,778)	16.2 (195,183)	15,9 (191,793)	15,8 (194,826)
MEPM*	16	8	12.4 (109,453)	11.8 (113,996)	10.7 (119,330)	14.4 123,976)	13.1 (180,850)	12.3 (201,991)	11.4 (206,368)	10.9 (209,149)	10.6 (217,161)	10.5 (214,691)	10.3 (218,610)
GM	16	16	7.0 (111,137)	6.1 (115,612)	5.3 (118,592)	5.1 (117,421)	4.5 (165,777)	4.1 (182,343)	3.3 (184,453)	2.9 (184,135)	3.1 (190,296)	3.0 (184,307)	2.8 (184,581)
AMK	64	64	3.1 (116,876)	2.6 (121,289)	2.1 (126,023)	1.9 (128,923)	1.5 (185,327)	1.3 (204,892)	1.1 (208,098)	0.9 (209,413)	0.9 (217,512)	0.8 (214,949)	0.7 (219,053)
LVFX	8	8	16.8 (111,005)	16.3 (115,478)	14.5 (119,162)	13.0 (120,691)	12.0 (174,301)	11.6 (193,366)	10.8 (197,890)	10.2 (199,760)	9.8 (207,963)	9.5 (204,829)	8.9 (207,311)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

-: Not under surveillance

* CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012) (M100-S22) Criteria was applied to determine BP after 2014.

v. *Acinetobacter* spp.

Table 6. Resistance rates (%) of *Acinetobacter* spp.

	BP	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PIPC	128	13.2 (19,125)	13.2 (19,433)	12.9 (20,183)	12.4 (20,223)	11.5 (27,887)	10.9 (29,776)	10.9 (27,468)	10.3 (27,905)	10.7 (26,237)	10.2 (23,018)	11.0 (22,399)
TAZ/PIPC	4/128	-	-	7.8 (4,953)	7.8 (5,215)	8.1 (9,058)	8.6 (10,551)	9.0 (10,983)	9.4 (12,171)	9.0 (12,401)	8.2 (11,478)	9.5 (11,275)
SBT/ABPC	16/32	6.5 (2,942)	7.2 (3,601)	5.8 (4,498)	5.2 (6,462)	4.8 (11,356)	5,4 (12,831)	4.7 (12,241)	4.4 (13,111)	4.3 (12,769)	3.4 (12,047)	3.6 (11,982)
CAZ	32	10.3 (19,672)	10.6 (20,067)	10.0 (20,856)	9.3 (20,852)	8.0 (28,166)	7.6 (29,844)	7.9 (27,308)	7.6 (28,077)	8.6 (26,614)	8.4 (23,626)	9.1 (23,064)
CFPM	32	10.4 (13,013)	10.5 (14,093)	9.2 (15,394)	7.6 (17,424)	7.2 (25,412)	7.4 (27,386)	7.6 (25,631)	6.8 (26,616)	6.8 (25,224)	7.0 (22,400))	7.2 (22,002)
IPM	16	2.2 (18,048)	2.0 (18,238)	2.3 (16,947)	3.6 (11,147)	3.2 (13,942)	3.1 (15,147)	2.5 (14,383)	2.0 (16,995)	1.8 (19,645)	1.1 (21,381)	1.1 (21,243)
MEPM	16	2.9 (15,485)	2.4 (15,880)	2.3 (17,027)	2.0 (18,859)	1.8 (28,227)	1.9 (30,489)	1.3 (28,064)	1.5 (29,024)	1.4 (27,418)	1.2 (24,163)	1.2 (23,500)
GM	16	9.6 (18,276)	10.2 (18,842)	9.5 (19,422)	8.9 (18,832)	8.5 (25,689)	8.5 (27,313)	8.2 (24,887)	7.8 (25,465)	8.0 (23,925)	7.7 (20,853)	8.6 (20,174)
AMK	64	4.5 (19,348)	4.5 (19,793)	3.5 (20,863)	3.6 (20,851)	3.1 (28,568)	2.3 (30,279)	2.3 (27,835)	2.0 (28,437)	2.1 (26,917)	2.0 (23,697)	2.4 (23,217)
LVFX	8	9.5 (18,732)	9.8 (19,484)	8.3 (20,040)	8.5 (20,047)	7.7 (27,858)	8.2 (29,702)	8.0 (27,360)	7.0 (28,209)	7.5 (26,898)	7.8 (23,650)	8.7 (22,998)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

-: Not under surveillance

2) Gram-positive bacteria

Source: JANIS

Looking at the recent status of gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for approximately 50% of all *Staphylococcus aureus*. Although the proportion has been declining over the past few years, it remains higher than that seen in other countries. The proportion is higher among medical institutions with fewer than 200 beds than among those with 200 or more (Table 10). In the case of enterococci, rising vancomycin (VCM) resistance is a problem in many countries, but as shown in Tables 11 and 12, levels in Japan are comparatively low, at less than 0.05% in the case of *Enterococcus faecalis* and 1.4% in *Enterococcus faecium*. However, also in 2021, the VCM resistance rate among *E. faecium* significantly increased, and widespread nosocomial outbreaks of VCM-resistant *E. faecium* have been observed in some regions. Regional changes in resistance rates will need to be kept under close observation. The proportion of penicillin-resistant *Streptococcus pneumoniae* (PRSP) accounted for approximately 40% of all detected pneumococcus in cerebrospinal fluid (CSF) samples, though the figure varies from year to year, because only around 100 CSF samples are tested (Table 13). The proportion of PRSP was low for non-CSF samples at below 1% (Table 14), and below 5% even adding penicillin intermediate resistant bacteria.

i. *Staphylococcus aureus*

Table 7. Resistance rates (%) of total *Staphylococcus aureus**

	BP	2018	2019	2020	2021
PCG	0.25	75.4 (287,805)	75.1 (295,031)	74.3 (281,583)	73.3 (277,317)
MPIPC	4	47.8 (266,047)	47.7 (265,763)	47.5 (243,162)	46.0 (237,103)
CFX	8	46.1 (57,604)	46.0 (64,239)	46.1 (61,811)	45.2 (62,331)
CEZ	32	20.7 (360,772)	19.7 (366,803)	19.3 (339,052)	17.8 (334,737)
GM	16	30.4 (345,964)	28.9 (350,425)	27.5 (325,197)	26.1 (317,744)
EM	8	51.7 (325,918)	51.2 (329,090)	50.5 (302,105)	48.4 (297,317)
CLDM	4	22.0 (340,953)	20.4 (350,136)	18.9 (325,568)	17.3 (319,298)
MINO	16	12.2 (377,507)	10.5 (385,264)	9.7 (360,076)	8.9 (353,680)
VCM	16	0.0 (374,982)	0.0 (382,254)	0.0 (356,747)	0.0 (347,976)
TEIC	32	<0.05 (336,502)	<0.05 (340,855)	<0.05 (314,742)	<0.05 (308,176)
LVFX	4	50.4 (358,941)	51.7 (368,676)	52.3 (344,943)	51.3 (339,292)
LZD	8	<0.05 (286,366)	<0.05 (294,735)	<0.05 (276,069)	<0.05 (268,079)
DAP	2	0.3 (72,401)	0.3 (98,366)	0.3 (108,416)	0.3 (116,811)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

*Data collection began in 2018.

-: Not under surveillance

Table 8. Resistance rates (%) of Methicillin-susceptible *Staphylococcus aureus* (MSSA)

	BP	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PCG	0.25	61.1 (68,839)	60.1 (75,025)	59.0 (82,477)	57.7 (86,314)	56.2 (119,343)	55.0 (126,394)	53.9 (129,943)	52.9 (135,360)	52.1 (138,818)	51.1 (133,767)	50.7 (135,944)
CEZ	32	0.3 (77,483)	<0.05 (84,520)	0.2 (93,945)	0.2 (103,603)	0.1 (146,254)	<0.05 (157,917)	<0.05 (161,831)	<0.05 (164,909)	<0.05 (167,084)	<0.05 (155,735)	<0.05 (159,135)
CVA/ AMPC	4/8	0.3 (11,696)	0.1 (9,466)	0.2 (11,230)	0.2 (11,666)	0.1 (19,163)	0.1 (21,783)	0.1 (24,713)	0.1 (26,376)	0.1 (25,258)	0.1 (24,967)	0.1 (26,846)
IPM	16	0.3 (74,636)	<0.05 (80,472)	0.2 (88,422)	0.2 (95,951)	<0.05 (136,878)	<0.05 (146,433)	<0.05 (149,014)	<0.05 (149,454)	<0.05 (150,811)	<0.05 (138,998)	<0.05 (137,863)
EM	8	22.7 (72,738)	23.4 (79,683)	24.0 (88,528)	23.8 (96,829)	22.9 (136,763)	23.3 (146,280)	23.5 (148,795)	23.1 (150,809)	22.7 (151,577)	22.6 (139,415)	21.5 (142,251)
CLDM	4	3.4 (67,523)	3.1 (74,387)	3.2 (83,914)	2.8 (93,467)	2.8 (136,292)	2.9 (148,439)	2.9 (151,841)	2.7 (155,141)	2.9 (157,700)	3.0 (147,257)	2.9 (150,416)
MINO	16	0.7 (77,872)	0.6 (84,595)	0.5 (94,425)	0.6 (104,145)	0.6 (151,493)	0.5 (163,214)	0.6 (167,178)	0.6 (169,953)	0.5 (171,857)	0.6 (161,001)	0.6 (164,230)
LVFX	4	9.3 (73,163)	10.2 (79,857)	10.6 (89,641)	10.7 (99,898)	11.6 (144,083)	12.3 (154,868)	13.1 (159,066)	13.8 (161,691)	14.7 (164,665)	15.5 (154,754)	15.9 (158,287)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

Table 9. Resistance rates (%) of Methicillin-resistant *Staphylococcus aureus* (MRSA)

	BP (2014-)	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
EM	8	91.3 (105,936)	90.6 (109,521)	88.4 (108,607)	86.0 (107,836)	84.1 (149,851)	83.8 (155,587)	82.9 (157,708)	81.7 (159,215)	80.7 (161,613)	79.8 (147,736)	78.6 (140,331)
CLDM	4	76.8 (102,895)	73.5 (106,124)	67.3 (105,503)	60.3 (106,910)	56.0 (153,329)	51.6 (160,500)	46.3 (164,301)	41.7 (169,049)	37.9 (175,081)	35.1 (161,937)	33.1 (153,027)
MINO	16	48.2 (117,325)	43.7 (120,321)	37.1 (120,300)	35.1 (121,258)	31.7 (173,983)	29.1 (182,306)	27.1 (185,770)	23.7 (189,813)	20.1 (195,422)	18.7 (181,557)	17.7 (172,374)
VCM	16	0.0 (115,679)	0.0 (119,111)	0.0 (119,441)	0.0 (120,535)	0.0 (172,083)	0.0 (181,288)	0.0 (185,948)	0.0 (189,853)	0.0 (195,332)	0.0 (181,671)	0.0 (171,879)
TEIC	32	<0.05 (110,380)	<0.05 (113,887)	<0.05 (113,684)	<0.05 (113,749)	<0.05 (158,233)	<0.05 (165,213)	<0.05 (167,342)	<0.05 (169,651)	<0.05 (173,090)	<0.05 (158,930)	<0.05 (150,589)
LVFX	4	89.0 (111,598)	88.3 (114,381)	86.8 (114,551)	85.4 (115,586)	85.2 (164,734)	85.8 (172,494)	86.5 (176,790)	86.8 (179,731)	87.8 (186,442)	88.5 (173,610)	88.9 (164,814)
LZD*	8	0.1 (76,632)	<0.05 (84,550)	<0.05 (85,223)	<0.05 (88,255)	0.1 (127,278)	<0.05 (136,468)	<0.05 (139,785)	<0.05 (144,332)	<0.05 (149,340)	<0.05 (137,980)	<0.05 (129,420)
DAP	2	-	-	-	1.1 (3,078)	0.9 (16,648)	0,8 (23,217)	0.7 (26,874)	0.5 (35,618)	0.4 (47,835)	0.5 (51,671)	0.5 (53,782)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

-: Not under surveillance

As of 2020, no VRSA had been reported.

* CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012) (M100-S22) Criteria was applied to determine BP after 2014.

Table 10. The proportion of (%) of patients with MRSA among all patients with *Staphylococcus aureus (S. aureus)*

Table 10-1. All participating medical institutions

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of medical institutions	594	660	745	883	1,435	1,653	1,795	1,947	2,075	2,167	2,220
Number of patients with MRSA	114,933	117,209	118,539	120,702	169,528	177,768	182,619	185,709	192,320	176,848	167,858
Number of patients with *S. aureus*	210,382	221,239	231,909	246,030	349,743	372,787	383,006	391,316	400,094	367,976	360,912
MRSA (%)*	54.6	53.0	51.1	49.1	48.5	47.7	47.7	47.5	48.1	48.1	46.5

Table 10-2. Participating medical institutions with 200 or more beds

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of medical institutions	-	-	-	791	1,177	1,269	1,312	1,334	1,357	1,364	1,378
Number of patients with MRSA	-	-	-	115,757	157,419	160,060	160,714	159,054	161,159	144,828	135,984
Number of patients with *S. aureus*	-	-	-	237,343	328,540	341,822	344,543	344,156	345,447	312,738	305,116
MRSA (%)*	-	-	-	48.8	47.9	46.8	46.6	46.2	46.7	46.3	44.6

Table 10-3. Participating medical institutions with fewer than 200 beds

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of medical institutions	-	-	-	92	258	384	483	613	718	803	842
Number of patients with MRSA	-	-	-	4,945	12,109	17,708	21,905	26,655	31,161	32,020	31,874
Number of patients with *S. aureus*	-	-	-	8,687	21,203	30,965	38,463	47,160	54,647	55,238	55,796
MRSA (%)*	-	-	-	56.9	57.1	57.2	57.0	56.5	57.0	58.0	57.1

Those detected in selective media were also included.

* The number of patients with MRSA / The number of patients with *S. aureus*

-: Not under surveillance

ii. *Enterococcus* spp.

Table 11. Resistance rates (%) of *Enterococcus faecalis*

	BP	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PCG	16	2.2 (53,290)	2.1 (60,342)	1.8 (65,220)	1.6 (67,324)	1.4 (92,132)	1.1 (98,465)	1.0 (98,478)	0.9 (104,023)	0.9 (107,021)	0.9 (111,226)	0.9 (114,014)
ABPC	16	0.4 (60,686)	0.4 (68,440)	0.3 (72,587)	0.3 (77,997)	0.3 (107,733)	0.2 (115,548)	0.2 (116,493)	0.2 (119,014)	0.2 (121,530)	0.2 (123,238)	0.2 (125,752)
EM	8	57.8 (53,222)	58.0 (60,825)	57.1 (64,465)	55.5 (69,171)	54.8 (95,409)	54.3 (101,036)	53.8 (101,379)	52.7 (102,496)	51.7 (102,871)	50.2 (103,067)	48.2 (105,505)
MINO	16	47.8 (61,549)	47.7 (69,421)	47.7 (74,880)	52.1 (81,925)	49.7 (115,648)	48.9 (123,860)	50.3 (125,728)	50.9 (128,160)	47.2 (130,729)	48.1 (133,174)	50.8 (135,820)
VCM	32	<0.05 (61,747)	<0.05 (69,719)	<0.05 (75,162)	<0.05 (81,867)	<0.05 (115,100)	<0.05 (124,305)	<0.05 (126,510)	<0.05 (129,545)	<0.05 (132,526)	<0.05 (135,184)	<0.05 (137,887)
TEIC	32	<0.05 (56,591)	<0.05 (63,747)	<0.05 (69,500)	<0.05 (76,160)	<0.05 (105,403)	<0.05 (112,636)	<0.05 (113,501)	<0.05 (115,397)	<0.05 (117,097)	<0.05 (118,367)	<0.05 (120,564)
LVFX	8	19.3 (58,877)	18.0 (65,934)	15.5 (70,895)	13.7 (77,563)	12.5 (109,160)	11.9 (117,297)	11.2 (120,136)	10.4 (122,551)	10.1 (125,836)	9.5 (128,449)	9.0 (131,088)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

Table 12. Resistance rates (%) of *Enterococcus faecium*

	BP	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PCG	16	86.9 (17,642)	87.4 (21,139)	87.7 (23,466)	86.9 (24,534)	87.6 (34,752)	88.2 (38,060)	87.8 (39,478)	87.5 (42,178)	87.4 (46,021)	86.9 (49,002)	87.1 (50,976)
ABPC	16	86.0 (19,780)	86.2 (23,885)	86.9 (26,199)	86.9 (28,564)	87.6 (41,459)	88.0 (45,069)	87.9 (47,046)	87.6 (49,207)	88.0 (52,929)	87.6 (54,632)	87.9 (56,395)
EM	8	87.2 (17,668)	88.1 (21,498)	85.9 (23,594)	84.5 (25,922)	84.5 (37,536)	84.0 (40,509)	83.1 (42,259)	83.0 (43,555)	83.1 (45,992)	83.1 (47,133)	80.0 (49,083)
MINO	16	26.9 (21,877)	28.8 (25,961)	29.3 (28,387)	32.2 (31,550)	35.1 (46,351)	34.7 (50,325)	36.2 (52,494)	38.3 (54,540)	33.0 (58,314)	31.7 (60,040)	30.2 (62,137)
VCM	32	1.0 (21,782)	0.4 (25,787)	0.7 (28,334)	0.7 (30,996)	0.7 (45,514)	0.9 (49,618)	0.8 (52,127)	0.9 (54,279)	1.5 (58,377)	1.4 (60,412)	2.6 (62,811)
TEIC	32	0.4 (20,163)	0.3 (23,855)	0.2 (26,282)	0.2 (29,151)	0.3 (41,905)	0.6 (45,388)	0.4 (47,321)	0.6 (48,991)	1.0 (52,502)	0.8 (54,125)	1.4 (55,948)
LVFX	8	82.9 (19,417)	83.4 (23,032)	84.5 (25,629)	84.7 (28,448)	85.8 (42,068)	86.6 (45,834)	86.5 (48.995)	86.7 (51,003)	87.6 (55,293)	86.9 (57,199)	87.2 (59,808)
LZD	8	0.0 (12,877)	0.1 (16,296)	<0.05 (18,561)	0.1 (22,044)	0.1 (33,382)	0.1 (37,099)	<0.05 (39,584)	0.1 (41.596)	0.1 (44,887)	0.1 (46,611)	0.1 (47,809)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

iii. *Streptococcus pneumoniae*

Table 13. Resistance rates (%) of *Streptococcus pneumoniae* (spinal fluid specimens)

	BP	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PCG	0.125	38.6 (101)	47.4 (97)	47.0 (83)	40.5 (126)	36.4 (140)	29.1 (117)	38.3 (94)	32.0 (100)	33.3 (57)	59.5 (42)
CTX	2	3.7 (82)	1.2 (84)	2.9 (69)	2.0 (100)	1.0 (105)	2.1 (97)	4.5 (88)	1.2 (85)	4.3 (47)	5.6 (36)
MEPM	1	4.2 (95)	2.2 (92)	1.2 (83)	4.2 (119)	0.7 (134)	5.0 (120)	2.1 (95)	1.0 (99)	6.0 (50)	6.8 (44)
EM	1	82.5 (80)	82.7 (81)	92.5 (67)	84.9 (86)	75.5 (98)	82.4 (91)	75.0 (76)	84.8 (79)	76.7 (43)	86.5 (37)
CLDM	1	53.8 (65)	68.7 (67)	65.1 (63)	62.7 83)	61.2 (98)	49.5 (91)	43.7 (71)	64.0 (75)	57.1 (42)	52.8 (36)
LVFX	8	0.0 (88)	0.0 (91)	1.3 (76)	0.0 (105)	0.0 (123)	0.9 (111)	2.3 (88)	0.0 (93)	0.0 (50)	0.0 (40)
VCM	2	0.0 (91)	0.0 (90)	0.0 (82)	0.0 (119)	0.0 (134)	0.0 (116)	0.0 (98)	0.0 (96)	0.0 (56)	0.0 (42)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

CLSI (2012) (M100-S22) Criteria was applied to determine BP.

Table 14. Resistance rates (other than spinal fluid specimens) (%) of *Streptococcus pneumoniae*

	BP	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PCG*	4	3.2 (24,980)	2.7 (26,932)	2.5 (27,206)	2.7 (36,475)	2.1 (35,960)	2.1 (34,415)	2.2 (33,483)	2.2 (31,506)	3.5 (16,056)	3.4 (16,526)
CTX	4	2.4 (21,654)	2.0 (23,096)	1.8 (23,002)	1.6 (30,734)	1.4 (29,405)	1.6 (27,773)	1.4 (27,004)	1.4 (26,040)	2.1 (13,140)	2.1 (13,878)
MEPM	1	6.9 (22,989)	5.1 (24,986)	5.4 (25,760)	5.0 (34,461)	5.7 (34,885)	6.0 (34,011)	6.3 (33,115)	6.4 (31,489)	8.9 (16,152)	8.9 (16,479)
EM	1	87.0 (21,979)	86.2 (22,435)	86.7 (22,215)	85.5 (30,501)	84.4 (30,144)	82.4 (28,097)	81.3 (27,154)	81.5 (26,270)	80.4 (13,529)	80.5 (14,352)
CLDM	1	56.4 (17,513)	56.1 (19,719)	57.1 (20,296)	56.1 (27,555)	54.1 (28,541)	50.5 (27,536)	49.9 (26,459)	50.9 (25,404)	49.5 (13,651)	49.5 (14,047)
LVFX	8	3.0 (24,105)	3.1 (25,764)	3.3 (26,236)	3.5 (35,457)	4.1 (35,431)	4.3 (34,241)	4.4 (33,551)	4.7 (32,057)	6.4 (16,499)	6.0 (16,818)
VCM	2	0.0 (24,085)	0.0 (25,425)	0.0 (25,775)	0.0 (33,530)	0.0 (33,670)	0.0 (32,681)	0.0 (31,741)	0.0 (30,250)	0.0 (15,625)	0.0 (16,176)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

* Each figure for PCG represents the sum of resistance (R: 8 μg/mL) and intermediate resistance (I: 4 μg/mL).

CLSI (2012) (M100-S22) Criteria was applied to determine BP.

3) Antimicrobial-resistant bacteria infection

Source: National Epidemiological Surveillance of Infectious Disease (NESID)

The numbers of cases reported under NESID each year through 2020 are publicized as confirmed reported data. Cases reported since 2013 are listed below. The scope of reporting is limited to cases where the isolated bacteria is regarded as the cause of an infectious disease, or cases where it was detected from specimens that normally should be aseptic. Colonization is excluded from the scope of reporting.

Among notifiable diseases (diseases that must be reported to the authorities in all cases), there have been around 80 reports of vancomycin-resistant enterococcal (VRE) infection per year since 2017, representing a slight rise from the trend of 50 to 60 reports per year between 2013 and 2016 Since 2017, the number of cases has been increasing, and in 2020 136 cases were reported which is the highest number since 1999 when reporting started. No case of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection has been reported since November 5, 2003, when this disease became notifiable. Carbapenem-resistant *Enterobacteriaceae* (CRE) infection became a notifiable disease on September 19, 2014, and in 2020 1,956 cases were reported, down from 2,333 in 2019. Surveillance for multiagent-resistant *Acinetobacter* (MDRA) infection was started in February 2011, with reporting of cases limited at first to designated sentinel sites. It subsequently became a notifiable disease on September 19, 2014, and reports ranged between 20 and 40 cases per year thereafter, with 10 cases reported in 2020.

Under a March 2017 notification issued by the Director of the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW, local public health institutes and other organizations have been using the PCR method to test strains isolated from notified cases of CRE infection for carbapenemase genes and other information. In 2020 results for 1380 strains were reported. The major carbapenemase gene was detected in 240 (17.4%) isolates, with the IMP form of the domestic carbapenemase gene accounting for the majority, 204 (85.0%). Bacterial species of the strains detected with IMP type and IMP genotypes showed similar regional characteristicssince 2017.

Looking at antimicrobial-resistant infections notified by Japan's approximately 500 designated sentinel sites (medical institutions that have 300 or more beds), both the number of reports of MRSA infections and the number of reports per sentinel site had decreased since 2011. The number of cases stopped falling during the period from 2016 to 2019, but in 2020, the number of cases decreased again to 14,940. Multidrug-resistant Pseudomonas aeruginosa (MDRP) infections had stopped falling during the period from 2017 to 2019 after a downward trend since 2013, but in 2020, the number of reported cases fell again to 116. Penicillin-resistant Streptococcus pneumoniae (PRSP) infections continued to decline in both the number of reports and the number of reports per sentinel.

i. Diseases subject to notifiable disease surveillance

Table 15. Number of cases reported for diseases subject to notifiable disease surveillance (2013-2020)

	2013	2014	2015	2016	2017	2018	2019	2020
VRE	55	56	66	61	83	80	80	136
VRSA	0	0	0	0	0	0	0	0
CRE	-	314*	1,673	1,573	1,660	2,289	2,333	1,956
MDRA	-	15*	38	33	28	24	24	10

* Reportable since September 19, 2014.

-: Not under surveillance

ii. Diseases reportable from designated sentinel sites

Table 16. Number of cases reported for diseases reportable from designated sentinel sites (2013-2020)

		2013	2014	2015	2016	2017	2018	2019	2020
PRSP	Total	3,161	2,292	2,057	2,017	2,001	1,895	1,754	879
	Per site	6.65	4.79	4.29	4.21	4.18	3.94	3.65	1.84
MRSA	Total	20,155	18,082	17,057	16,338	16,551	16,311	16,241	14,940
	Per site	42.43	37.83	35.61	34.11	34.55	33.91	33.84	31.19
MDRA*	Total	8	4	-	-	-	-	-	-
	Per site	0.02	0.01	-	-	-	-	-	-
MDRP	Total	319	268	217	157	128	121	127	116
	Per site	0.67	0.56	0.45	0.33	0.27	0.25	0.26	0.24

* MDRA became reportable under notifiable disease surveillance on September 19, 2014.

-: Not under surveillance

4) Other antimicrobial-resistant bacteria

i. *Campylobacter* spp.

Source: Tokyo Metropolitan Institute of Public Health

Tokyo Metropolitan Institute of Public Health has conducted trend surveillance concerning the proportion of antimicrobial-resistant *Campylobacter* spp. Among the 83 outbreaks of food-borne illness that occurred in Tokyo in 2021, 19 outbreaks (22.9%) were caused by *Campylobacter* spp., being the largest cause of bacterial food-borne illness since 2005.[1] The target strains were *Campylobacter jejuni* and *Campylobacter coli* isolated from sporadic diarrhea patients in Tokyo. Resistance rates for 2011-2020 are shown in the tables. The resistance rate of *Campylobacter jejuni* (*C. jejuni*) to ciprofloxacin (CPFX) was 34.1%, lower than 2019. The erythromycin (EM) resistant strain was not detected. The resistance rate of CPFX to *Campylobacter coli* was 57.1%, which was lower than the previous year. In both cases, the resistance rate has remained largely unchanged, although it has increased or decreased from year to year. However, the number of tested strains was smaller for *Campylobacter coli*, and this should be taken into consideration upon interpretation of the result.

Table 17. Resistance rates (%) of *Campylobacter jejuni* * from sporadic diarrhea

(Number of samples)	2011 (108)	2012 (83)	2013 (85)	2014 (125)	2015 (116)	2016 (113)	2017 (115)	2018 (110)	2019 (132)	2020 (86)
EM	3.7	2.4	1.2	0.8	0.9	0.9	1.7	1.8	3.0	0.0
NA	53.7	62.7	50.6	50.4	37.1	53.1	46.1	51.7	54.5	31.4
CPFX	53.7	62.7	50.6	50.4	37.1	52.2	43.5	51.8	54.5	31.4

* Strains isolated from diarrhea cases in Tokyo

Prepared from [5] with partial modification.

Table 18. Resistance rates (%) of *Campylobacter coli* * from sporadic diarrhea

(Number of samples)	2011 (8)	2012 (9)	2013 (12)	2014 (7)	2015 (8)	2016 (14)	2017 (8)	2018 (8)	2019 (16)	2020 (7)
EM	12.5	22.2	16.7	28.6	0.0	14.3	25.0	62.5	25.0	28.6
NA	87.5	66.7	75.0	57.1	50.0	50.0	62.5	50	68.8	57.1
CPFX	87.5	66.7	75.0	57.1	50.0	35.7	62.5	37.5	68.8	57.1

* Strains isolated from diarrhea cases in Tokyo

Prepared from [5] with partial modification.

ii. Non-typhoidal *Salmonella* spp.

Source: Public Health Institutes

The 21 Public Health Institutes across Japan conducted research on the multiagent-resistant status of the 2,948 *Salmonella* strains that were isolated between 2015 and 2021, using standardized methodology.[2] Table 19 lists the key serotypes of human-derived strains and food-derived strains.

In total, 39.2% of the 2,093 human-derived strains and 91.3% of the 855 food-derived strains indicated resistance to one or more of the 17 antimicrobials used in the study (Tables 20 and 21). Although this investigation was not conducted as a routine national surveillance operation, this was nationwide surveillance and the resistance rates of the strains isolated between 2015 and 2020 are considered to reflect the current status in Japan. In this reporting period (2021), 46 (31.5%) of 146 human-derived strains and 121 (86.4%) of 140 food-derived strains were resistant to one or more agents, which did not differ significantly from the resistance rates of 1,947 human-derived strains (39.8%) and 715 food-derived strains (91.0%), which were isolated between 2015 and 2020. As for multiagent resistance, the proportion of three-agent resistance was large both among human-derived strains and among food-derived strains. Thirty-nine among human-derived strains, and 66 among food-derived strains, indicated multiagent resistance to as many as 6 to 11 agents. In addition, resistant strains to meropenem (MEPM) were detected for the first time in human-derived isolates in 2020 (Table 20). This isolate (1 strain) was *S.* Heidelberg, a multiagent-resistant strain resistant to eight agents, including MEPM.

Tables 22 and 23 show antimicrobial resistance in the top two serotypes of food-derived strains (*S.* Infantis and *S.* Schwarzengrund), while Tables 24 to 28 show antimicrobial resistance in the top five serotypes of human-derived strains (*S.* Infantis, *S.* Enteritidis, *S.* Thompson, *S.* 4:i:-, and *S.* Saintpaul). Among food-derived strains, *S.* Schwarzengrund accounted for a higher proportion of isolates in the current period (2021) than in 2015-2020, but the resistance trends were not significantly different. In human-derived strains, on the other hand, as resistance trends were observed characteristic to each serotype, the resistance rates were compared by serotype over time.

Three serotypes (S. Schwarzengrund, S. Infantis and S. Manhattan) are found commonly in both the top 10 human-derived and top 5 food-derived serotypes, and the antimicrobial resistance rates of these three serotypes were compared between human- and food-derived strains (Table 29). Clear similarities were observed in overall resistance trends to various antimicrobials, suggesting a strong association between human-derived resistant strains (approximately 40% of S. Infantis and the majority of *S.* Schwarzengrund and *S.* Manhattan) and food-derived

resistant strains.

In addition to antimicrobial susceptibility tests, strains isolated between 2015 and 2020 that demonstrated resistance to one or more of the agents cefotaxime (CTX), ceftazidime (CAZ), and cefoxitin (CFX) (41 human-derived strains and 46 food-derived strains) underwent testing to detect extended-spectrum beta-lactamase (ESBL) and AmpC beta-lactamase (AmpC)

producing genes. The CTX-M-1 group was the most common genotype among the ESBL producing genes in human-derived and food-derived strains alike, followed by TEM. CIT was the most common genotype among the AmpC producing genes in human-derived and food-derived strains alike, followed by TEM. These results showed similarities in trends toward the detection of ESBL and AmpC genes in both human-derived and food-derived strains, while the CTX-M-9 group (ESBL-producing genes) was detected only in human-derived strains, and the EBC type (AmpC genes) was detected only in food-derived strains. Strain characteristic detections were also observed.

Table 19. Serotypes of human- and food-derived non-typhoidal *Salmonella* spp. (2015-2021)

Human-derived strains (n=2,093)	%	Food-derived strains (n=855)	%
Enteritidis	12.7	Schwarzengrund	52.5
4:i:-	11.1	Infantis	22.9
Infantis	9.4	Manhattan	7.6
Thompson	8.0	Heidelberg	2.1
Saintpaul	6.3	Agona	2.1
Typhimurium	6.3	Others	12.8
Schwarzengrund	5.3	Total	100.0
Newport	2.9		
Stanley	2.9		
Manhatten	2.3		
Others	32.9		
Total	100.0		

Table 20. Resistance rates of human-derived non-typhoidal *Salmonella* spp. (2015-2021)

	2015 (n=387)	2016 (n=360)	2017 (n=409)	2018 (n=315)	2019 (n=265)	2020 (n=211)	2021 (n=146)	SUM (n=2093)
ABPC	17.3	18.1	15.6	19.4	14.7	14.7	12.3	16.5
GM	0.3	0.6	0.7	0.6	1.5	0.5	0.7	0.7
KM	5.9	11.7	7.3	8.3	6.4	6.2	7.5	7.7
SM	27.4	30.0	26.4	29.2	23.8	25.6	21.9	26.9
TC	32.6	29.2	27.1	25.4	22.6	26.1	21.9	27.2
ST	4.4	6.7	7.8	6.3	3.4	9.0	4.8	6.1
CP	2.3	6.4	5.1	6.0	5.3	5.2	5.5	5.0
CTX	0.3	2.5	3.2	3.2	1.5	0.9	2.1	2.0
CAZ	0.3	2.2	1.7	1.9	0.8	0.9	1.4	1.3
CFX	0.0	1.4	0.5	0.6	0.0	0.9	1.4	0.6
FOM	0.0	0.3	0.2	0.3	0.4	0.5	0.0	0.2
NA	7.0	8.1	8.8	5.7	4.2	5.2	5.5	6.7
CPFX	0.3	0.8	1.7	0.3	0.4	0.0	1.4	0.7
NFLX	0.3	0.8	0.5	0.0	0.8	0.0	0.0	0.4
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0
Number resistant to one or more antimicrobials	164	161	152	125	89	83	46	820
Proportion resistant to one or more antimicrobials	42.4	44.7	37.2	39.7	33.6	39.3	31.5	39.2

Table 21. Resistance rates of food-derived non-typhoidal *Salmonella* spp.* (2015-2021) (%)

	2015 (n=156)	2016 (n=110)	2017 (n=86)	2018 (n=108)	2019 (n=126)	2020 (n=129)	2021 (n=140)	SUM (n=855)
ABPC	17.9	13.6	11.6	12.0	11.1	12.4	5.0	12.0
GM	0.0	0.9	1.2	0.0	0.0	0.0	0.7	0.4
KM	48.1	47.3	45.3	50.0	57.1	65.9	62.9	54.4
SM	82.7	70.9	69.8	77.8	64.3	70.5	71.4	72.9
TC	85.9	76.4	73.3	78.7	70.6	82.9	80.7	78.9
ST	19.9	16.4	12.8	38.0	25.4	24.8	14.3	21.9
CP	7.1	10.0	2.3	8.3	4.0	7.0	4.3	6.2
CTX	5.1	5.5	8.1	6.5	6.3	4.7	1.4	5.1
CAZ	4.5	6.4	8.1	6.5	4.8	3.9	0.0	4.6
CFX	2.6	3.6	8.1	4.6	5.6	5.4	1.4	4.3
FOM	0.0	0.9	1.2	0.0	0.0	0.0	0.0	0.2
NA	18.6	18.2	14.0	16.7	27.0	23.3	20.0	20.0
CPFX	0.0	0.9	1.2	0.0	0.0	0.0	0.0	0.2
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4
Number resistant to one or more antimicrobials	143	96	77	98	113	124	121	772
Proportion resistant to one or more antimicrobials	91.7	87.3	89.5	90.7	89.7	96.1	86.4	90.3

Figures in parentheses indicate resistance rate in strains isolated from domestic chicken meat.

Table 22. Resistance rates of food-derived *S*. Infantis (2015-2021) (%)

	2015 (n=65)	2016 (n=33)	2017 (n=19)	2018 (n=27)	2019 (n=24)	2020 (n=8)	2021 (n=20)	SUM (n=196)
ABPC	10.8	12.1	5.3	14.8	8.3	37.5	10.0	11.7
GM	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.5
KM	46.2	42.4	15.8	33.3	37.5	62.5	35.0	39.3
SM	81.5	72.7	68.4	85.2	58.3	50.0	60.0	73.0
TC	89.2	81.8	68.4	85.2	58.3	37.5	70.0	77.6
ST	18.5	30.3	0.0	44.4	12.5	0.0	30.0	21.9
CP	3.1	3.0	0.0	0.0	0.0	12.5	5.0	2.6
CTX	4.6	6.1	5.3	11.1	8.3	12.5	0.0	6.1
CAZ	3.1	9.1	5.3	11.1	0.0	12.5	0.0	5.1
CFX	4.6	9.1	5.3	14.8	8.3	25.0	5.0	8.2
FOM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NA	3.1	9.1	0.0	3.7	16.7	0.0	15.0	6.6
CPFX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 23. Resistance rates of food-derived *S*. Schwarzengrund (2015-2021) (%)

	2015 (n=47)	2016 (n=38)	2017 (n=45)	2018 (n=51)	2019 (n=66)	2020 (n=95)	2021 (n=107)	SUM (n=449)
ABPC	17.0	5.3	0.0	7.8	3.0	5.3	1.9	5.1
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	85.1	86.8	77.8	80.4	92.4	73.7	72.0	79.5
SM	93.6	78.9	82.2	76.5	74.2	80.0	73.8	78.8
TC	95.7	84.2	80.0	86.3	81.8	93.7	83.2	86.6
ST	36.2	18.4	24.4	56.9	43.9	30.5	12.1	30.1
CP	19.1	13.2	4.4	9.8	6.1	5.3	4.7	7.8
CTX	0.0	0.0	2.2	0.0	0.0	1.1	0.9	0.7
CAZ	0.0	0.0	2.2	0.0	0.0	0.0	0.0	0.2
CFX	0.0	0.0	2.2	0.0	0.0	1.1	0.0	0.4
FOM	0.0	2.6	2.2	0.0	0.0	0.0	0.0	0.4
NA	25.5	21.1	6.7	23.5	27.3	20.0	18.7	20.5
CPFX	0.0	2.6	0.0	0.0	0.0	0.0	0.0	0.2
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 24. Resistance rates of human-derived *S*. Infantis (2015-2021) (%)

	2015 (n=34)	2016 (n=48)	2017 (n=48)	2018 (n=22)	2019 (n=16)	2020 (n=19)	2021 (n=9)	SUM (n=196)
ABPC	0.0	2.1	0.0	9.1	6.3	5.3	0.0	2.6
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	20.6	14.6	6.3	22.7	12.5	5.3	11.1	13.3
SM	29.4	33.3	20.8	50.0	31.3	26.3	22.2	30.1
TC	47.1	33.3	22.9	54.5	37.5	47.4	22.2	36.7
ST	14.7	14.6	2.1	18.2	0.0	21.1	0.0	10.7
CP	0.0	0.0	0.0	9.1	6.3	5.3	0.0	2.0
CTX	0.0	0.0	0.0	4.5	6.3	5.3	0.0	1.5
CAZ	0.0	0.0	0.0	0.0	0.0	5.3	0.0	0.5
CFX	0.0	2.1	0.0	0.0	0.0	5.3	0.0	1.0
FOM	0.0	0.0	0.0	0.0	6.3	0.0	0.0	0.5
NA	8.8	4.2	8.3	0.0	12.5	5.3	11.1	6.6
CPFX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 25. Resistance rates of human-derived *S*. Enteritidis (2015-2021) (%)

	2015 (n=39)	2016 (n=41)	2017 (n=50)	2018 (n=43)	2019 (n=37)	2020 (n=35)	2021 (n=20)	SUM (n=265)
ABPC	5.1	19.5	6.0	7.0	5.4	0.0	0.0	6.8
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	2.6	2.4	0.0	0.0	0.0	0.0	0.0	0.8
SM	12.8	12.2	14.0	14.0	5.4	2.9	0.0	9.8
TC	10.3	2.4	6.0	9.3	5.4	2.9	0.0	5.7
ST	5.1	0.0	0.0	0.0	0.0	5.7	0.0	1.5
CP	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.4
CTX	0.0	2.4	0.0	0.0	0.0	0.0	5.0	0.8
CAZ	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.4
CFX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FOM	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.4
NA	10.3	26.8	14.0	25.6	10.8	14.3	15.0	17.0
CPFX	0.0	0.0	0.0	0.0	0.0	0.0	5.0	0.4
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 26. Resistance rates of human-derived *S*. Saintpaul (2015-2021) (%)

	2015 (n=27)	2016 (n=26)	2017 (n=42)	2018 (n=10)	2019 (n=8)	2020 (n=12)	2021 (n=7)	SUM (n=132)
ABPC	7.4	7.7	14.3	10.0	0.0	8.3	0.0	9.1
GM	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.8
KM	0.0	3.8	4.8	0.0	0.0	0.0	0.0	2.3
SM	3.7	3.8	11.9	0.0	0.0	8.3	0.0	6.1
TC	40.7	15.4	21.4	10.0	12.5	25.0	14.3	22.7
ST	0.0	11.5	16.7	10.0	12.5	8.3	0.0	9.8
CP	3.7	0.0	14.3	0.0	12.5	0.0	0.0	6.1
CTX	0.0	0.0	11.9	0.0	0.0	0.0	0.0	3.8
CAZ	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.8
CFX	0.0	3.8	0.0	0.0	0.0	0.0	0.0	0.8
FOM	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.8
NA	7.4	3.8	19.0	0.0	0.0	0.0	0.0	8.3
CPFX	3.7	0.0	9.5	0.0	0.0	0.0	0.0	3.8
NFLX	3.7	0.0	0.0	0.0	0.0	0.0	0.0	0.8
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 27. Resistance rates of human-derived *S*. 4:i:- (2015-2021) (%)

	2015 (n=60)	2016 (n=37)	2017 (n=36)	2018 (n=36)	2019 (n=23)	2020 (n=24)	2021 (n=17)	SUM (n=233)
ABPC	71.7	64.9	77.8	86.1	82.6	79.2	76.5	76.0
GM	1.7	0.0	2.8	0.0	0.0	0.0	0.0	0.9
KM	3.3	5.4	2.8	8.3	4.3	4.2	11.8	5.2
SM	73.3	70.3	80.6	91.7	82.6	70.8	70.6	77.3
TC	85.0	62.2	77.8	80.6	65.2	50.0	76.5	73.4
ST	5.0	10.8	5.6	8.3	8.7	0.0	5.9	6.4
CP	3.3	10.8	8.3	13.9	8.7	4.2	11.8	8.2
CTX	0.0	2.7	2.8	2.8	0.0	0.0	0.0	1.3
CAZ	0.0	2.7	2.8	0.0	0.0	0.0	0.0	0.9
CFX	0.0	0.0	2.8	0.0	0.0	0.0	0.0	0.4
FOM	0.0	2.7	0.0	0.0	0.0	0.0	0.0	0.4
NA	1.7	2.7	5.6	0.0	0.0	0.0	0.0	1.7
CPFX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 28. Resistance rates of human-derived *S*. Thompson (2015-2021) (%)

	2015 (n=28)	2016 (n=28)	2017 (n=30)	2018 (n=29)	2019 (n=27)	2020 (n=11)	2021 (n=14)	SUM (n=167)
ABPC	0.0	10.7	0.0	0.0	7.4	0.0	0.0	3.0
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	7.1	0.0	0.0	0.0	0.0	0.0	0.0	1.2
SM	7.1	7.1	3.3	6.9	0.0	0.0	7.1	4.8
TC	3.6	7.1	6.7	0.0	0.0	0.0	0.0	3.0
ST	0.0	7.1	0.0	0.0	0.0	0.0	0.0	1.2
CP	0.0	7.1	0.0	0.0	0.0	0.0	0.0	1.2
CTX	0.0	10.7	0.0	0.0	0.0	0.0	0.0	1.8
CAZ	0.0	7.1	0.0	0.0	0.0	0.0	0.0	1.2
CFX	0.0	7.1	0.0	0.0	0.0	0.0	0.0	1.2
FOM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NA	0.0	0.0	0.0	3.4	0.0	0.0	0.0	0.6
CPFX	0.0	7.1	0.0	0.0	0.0	0.0	0.0	1.2
NFLX	0.0	7.1	0.0	0.0	0.0	0.0	0.0	1.2
AMK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 29. Resistance rates of *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan detected in humans and food (2015-2021) (%)

	Infantis		**Schwarzengrund**		**Manhattan**	
	Human (n=196)	Food (n=196)	Human (n=110)	Food (n=449)	Human (n=49)	Food (n=65)
ABPC	2.6	11.7	2.7	5.1	2.0	12.3
GM	0.0	0.5	0.0	0.0	0.0	0.0
KM	13.3	39.3	63.6	79.5	0.0	0.0
SM	30.1	73.0	68.2	78.8	89.8	95.4
TC	36.7	77.6	68.2	86.6	85.7	80.0
ST	10.7	21.9	25.5	30.1	0.0	3.1
CP	2.0	2.6	1.8	7.8	0.0	0.0
CTX	1.5	6.1	1.8	0.7	0.0	10.8
CAZ	0.5	5.1	1.8	0.2	0.0	10.8
CFX	1.0	8.2	0.0	0.4	0.0	1.5
FOM	0.5	0.0	0.0	0.4	0.0	0.0
NA	6.6	6.6	12.7	20.5	8.2	13.8
CPFX	0.0	0.0	0.0	0.2	0.0	1.5
NFLX	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0

iii. *Neisseria gonorrhoeae*

Source: National Institute of Infectious Diseases

The 618, 675, 982, 1,167, and 1,023, 825 and 698 *Neisseria gonorrhoeae* strains that were respectively isolated between 2015 and 2021 were tested for antimicrobial susceptibility (based on EUCAST breakpoints; Table 30). Ceftriaxone (CTRX)-resistant strains respectively accounted for 6.2%, 4.3%, 4.3%, 3.5%, 5.4%, 2.7% and 0.7% since 2015. Strains assessed as resistant based on the CLSI Criteria (MIC ≥ 0.5 μg/mL) accounted for 0.6%, 0.4%, 0.5%, 0.3%, and 0.4% since 2015 but were not observed in 2020 and 2021. No spectinomycin (SPCM)-resistant strains were present. On the other hand, the resistance rate of azithromycin (AZM) was 13.0% in 2015 and shifted between 33% and 43.9% from 2016 to 2020. It was 11.6% in 2021.

The CLSI Criteria do not provide a resistance breakpoint for AZM, but, using the azithromycin (AZM) MIC distribution of strains with the 23S rRNA gene mutation as the basis, strains with a MIC of 2 μg/mL or higher are referred to as "non-wild-type." When we investigated the resistance rate (see Reference (8)), albeit as a reference, we found that, between 2015 and 2021, 3.2%, 4.0%, 4.0%, 6.3%, 7.5%, 7.0% and 6.7% of strains, respectively, had a MIC of 2 μg/mL or higher, indicating an upward trend. According to clinical assessments in Japan, strains indicating an AZM MIC of 1 μg/mL or higher can reasonably be regarded as resistant. Under this criterion (R ≥ 1 μg/mL), azithromycin-resistant strains accounted for 11.0%, 9.3%, 11.2%, 15.9%, 14.9%, 14,3% and 11.5% of strains respectively between 2015 and 2021. Among the other three antimicrobials, the proportion of cefixime (CFIX)- resistant strains accounted for approximately 20-40%, and that of CPFX-resistant strains accounted for approximately 60-80%. Benzylpenicillin (PCG) would not have a therapeutic effect on more than 80% of strains.

Table 30. Resistance rates of *Neisseria gonorrhoeae* (%)

	2015 (618 株)	2016 (675 株)	2017 (982 株)	2018 (1167 株)	2019 (1023 株)	2020 (825 株)	2021 (698 株)
CTRX	6.2	4.3	4.3	3.5	5.4	2.7	0.7
SPCM	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AZM	13.0	33.5	42.6	43.9	40.1	40.2	11.6
PCG*	38.4(96.6)	36.3(96.9)	37.8(99.0)	31.7(82.5)	35.8(88.5)	37.1(98.9)	23.5 (92.7)
CFIX	36.2	43.2	31.0	28.4	33.4	33.1	21.9
CPFX	79.5	78.0	75.8	66.9	64.6	71.2	75.6

The EUCAST (Appendix 8) standards were used for susceptibility and resistance assessment.

* Figures in parentheses indicate the sum of resistance and intermediate resistance.

The EUCAST resistance breakpoints are as follows. CTRX (>0.125 μg/mL), SPCM (> 64 μg/mL), AZM (>0.5 μg/mL), PCG (> 1 μg/mL), CFIX (>0.125 μg/mL), CPFX (> 0.06 μg/mL)

iv. *Salmonella* Typhi, *Salmonella* Paratyphi A, *Shigella* spp.

Source: National Institute of Infectious Diseases

The 3-46 *Salmonella* Typhi strains that were isolated between 2015 and 2021 were tested for antimicrobial susceptibility. CPFX-non-susceptible strains accounted for 55.0-100.0%, while strains with advanced resistance (MIC ≥ 4) to ciprofloxacin accounted for 5.9-25.0%. During this period, 15 strains of multiagent-resistant *Salmonella* Typhi that indicated resistance to ampicillin (ABPC), chloramphenicol (CP) and sulfamethoxazole-trimethoprim (ST) were isolated, along with five strains of CTX-resistant *Salmonella* Typhi.

The 0-30 *Salmonella* Paratyphi A strains isolated between 2015 and 2021 were tested for antimicrobial susceptibility. CPFX-non-susceptible strains accounted for 76.9-100% and one strain with advanced CPFX resistance (MIC ≥ 4) was isolated. No cefotaxime-resistant strains were isolated among the *Salmonella* Paratyphi A.

The 2-156 *Shigella* spp. strains that were isolated between 2015 and 2021 were tested for antimicrobial susceptibility. ST-resistant strains accounted for 50.0-91.9%; CPFX-non-susceptible strains for 0.0-45.7%; and cefotaxime-resistant strains for 0.0-27.0%.

Table 31. Resistance rates of *Salmonella* Typhi (%)

	2015 (n=32)	2016 (n=46)	2017 (n=31)	2018 (n=34)	2019 (n=28)	2020 (n=20)	2021 (n=3)
ABPC	5.7	2.2	12.9	2.9	10.7	20.0	0.0
CP	5.7	2.2	12.9	5.9	10.7	25.0	0.0
ST	5.7	2.2	12.9	5.9	10.7	25.0	0.0
NA	68.8	63.0	83.9	61.7	57.1	55.0	66.7
CPFX	68.8(12.5*)	63.0(23.9*)	83.9(16.1*)	61.7(5.9*)	60.7(10.7*)	65.0(25.0*)	100.0(0.0*)
CTX	0.0	0.0	0.0	2.9	3.6	15.0	0.0

* Advanced resistance to fluoroquinolone

Table 32. Resistance rates of *Salmonella* Paratyphi A (%)

	2015 (n=30)	2016 (n=20)	2017 (n=13)	2018 (n=21)	2019 (n=16)	2020 (n=5)	2021 (n=0)
ABPC	0.0	0.0	0.0	0.0	0.0	0.0	-
CP	0.0	0.0	0.0	0.0	0.0	0.0	-
ST	0.0	0.0	0.0	0.0	0.0	0.0	-
NA	80.0	80.0	76.9	100.0	87.5	100.0	-
CPFX	83.3	83.3	76.9	100.0	87.5	100.0	-
CTX	0.0	0.0	0.0	0.0	0.0	0.0	-

Table 33. Resistance rates of *Shigella* spp. (%)

	2015 (n=105)	2016 (n=73)	2017 (n=91)	2018 (n=156)	2019 (n=91)	2020 (n=74)	2021 (n=2)
ABPC	21.9	42.5	31.9	19.2	14.3	41.9	50.0
CP	11.4	24.7	26.4	9.0	6.6	4.1	50.0
ST	81.0	80.8	73.6	76.9	76.9	91.9	50.0
NA	63.8	52.1	52.8	45.5	33.0	83.8	50.0
CPFX	45.7	35.6	35.2	21.2	14.3	35.1	0.0
CTX	5.7	16.4	13.2	5.1	3.3	27.0	0.0

5) Mycobacterium tuberculosis

Source: The Research Institute of Tuberculosis, Japan Anti-tuberculosis Association

Looking at major antituberculosis antibiotics—isoniazid (INH), rifampicin (RFP), and ethambutol (EB)—among patients with culture-positive pulmonary tuberculosis who were newly notified between 2011 and 2021, resistance to INH has been on the rise in recent years, while RFP and EB resistance rates have remained mostly at the same level. Although a rise of up to 1.1 percentage points was seen in streptomycin (SM) resistance in 2017, it has mostly remained at the same level since 2018. The number of newly reported cases with multiagent-resistant tuberculosis that are resistant at least to both INH and RFP remained in the range of approximately 50 to 60 (0.4-0.9%) per year.

Table 34. Newly Notified Patients with Culture-positive Pulmonary Tuberculosis: Trends in Agent Susceptibility at the Time of Notification

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Culture-positive patients, N	10,915	11,261	10,523	10,259	10,035	9,878	9,580	9,016	8,110	6,645	5,902
INH-resistant, n (%)*	386 (4.8)	380 (4.6)	369 (4.8)	349 (4.6)	372 (4.9)	369 (4.8)	383 (4.9)	377 (5.0)	359 (5.4)	297 (5.7)	221 (4.9)
RFP-resistant, n (%)*	86 (1.1)	73 (0.9)	64 (0.8)	76 (1.0)	77 (1.0)	74 (1.0)	80 (1.0)	87 (1.1)	65 (1.0)	60 (1.2)	56 (1.2)
INH & RFP-resistant†, n (%)*	60 (0.7)	60 (0.7)	47 (0.4)	56 (0.5)	48 (0.5)	49 (0.6)	52 (0.7)	55 (0.6)	44 (0.7)	46 (0.9)	41 (0.9)
SM-resistant, n (%)§	-	509 (6.1)	475 (6.2)	469 (6.2)	476 (6.3)	461 (6.0)	557 (7.1)	471 (6.3)	428 (6.5)	356 (6.9)	287 (6.4)
EB-resistant, n (%)¶	-	151 (1.8)	106 (1.4)	130 (1.7)	129 (1.7)	100 (1.3)	106 (1.3)	130 (1.7)	126 (1.9)	78 (1.5)	79 (1.9)

* The denominator was defined as the number of patients with recorded INH- and RFP-susceptibility testing results among all culture- positive patients: 8,046 (73.7%) patients in 2011, 8,347 (74.1%) patients in 2012, 7,701 (73.2%) patients in 2013, 7,645 (74.5%) patients in 2014, 7,630 (76.0%) patients in 2015, 7,732 (78.3%) patients in 2016, 7,891 (82.4%) patients in 2017, 7,570 (84.0%) patients in 2018, 6,658 (82.1%) patients in 2019, 5,209（78. 4%） patients in 2020, and 4,551 patients in 2021.

-: Not under surveillance

† INH- and RFP- resistant tuberculosis bacteria are referred to as "multiagent-resistant."

§ The proportion appeared here showed the share in patients with INH- and RFP-susceptibility testing results, excluding those who were not tested for SM-susceptibility or those with the unknown test result: 54 patients in 2012, 48 patients in 2013, 52 patients in 2014, 48 patients in 2015, 47 patients in 2016, 51 patients in 2017, 47 patients in 2018, 41 patients in 2019, 38 patients in 2020, and 36 patients in 2021.

¶ The proportion appeared here showed the share in patients with INH- and RFP-susceptibility testing results, excluding those who were not tested for EB-susceptibility or those with the unknown test result: 14 in 2012, 13 in 2013, 13 in 2014, 19 in 2015, 17 in 2016, 14 in 2017, 13 in 2018, 8 in 2019, 14 in 2020, and 9 patients in 2021.

6) *Clostridioides difficile* infection

Clostridioides difficile (CDI) is a spore-forming gram-positive anaerobic bacillus that colonizes the intestines of about 10% of healthy adults.[3] CDI is a major healthcare-associated infection that causes diarrhea at hospitals and long-term care facilities for the elderly. In addition, CDI has been recognized as a cause of diarrhea even in the community.[4]

Existing observational studies in Japan indicate that the CDI incidence rate in Japan is 0.8-4.7 cases per 10,000 patient days, while prevalence is 0.3-5.5 cases per 1,000 admissions.[5] In a multi-institutional prospective study (20 wards at 12 institutions) using toxigenic cultures and nucleic acid amplification tests (NAAT), the CDI incidence rate was 7.4 cases per 10,000 patient days, rising to 22.2 in ICU wards, suggesting that the incidence rate is higher than indicated by existing reports, with a particularly high risk in ICU wards.[6] Comparison of prevalence rates among hospitals and with other countries should take into account the influence of specimen collection wards, testing methods, definition of relapse, differences in average length of hospital stay, and other factors.

Since 2019, the AMR Clinical Reference Centre (AMRCRC) has been operating the J-SIPHE, preparing annual reports, and started investigating CDI trends. The number of CDI outbreaks per 10,000 patient hospital days (n in the table is the number of facilities, and the distribution of occurrences per facility (number of occurrences/total number of patients in hospital x 10,000) is shown) showed a decreasing trend: in 2019, 1.38 (IQR: 0.56-2.43) in 276 facilities; in 2020, 1.20 (IQR: 0.45-2.13) in 347 facilities; and in 2021, 0.96 (IQR: 0.32-1.97) in 470 facilities. Changes in characteristics at participating facilities and the impact of the COVID-19 pandemic need to be considered.

Table 35. Distribution of *Clostridioides difficile* outbreaks in hospitals (outbreaks per 10,000 patient hospital days)

	2019(n=276)*	2020(n=347)**	2021 (n=470)
Clostridioides difficile (IQR)	1.38(0.56-2.43)	1.20(0.45-2.13)	0.96 (0.32-1.97)

"n" in the table is the number of facilities, and the distribution of occurrences per facility (number of occurrences/total number of patients in hospital x 10,000)

*2019 included 253 facilities for toxin testing using immunochromatography, 3 facilities for testing using NAAT method, and 20 other facilities.

**81 facilities were included in 2020 and 65 facilities in 2021 where only toxin is confirmed by immunochromatography, and CDI is determined when tested positive. 8 facilities were included in 2020 and 2 facilities in 2021 where only toxin is confirmed by immunochromatography, and CDI is determined when tested positive / toxin is tested by immunochromatography using cultured colony when tested negative, and test is discontinued when both tested negative. 115 facilities were included in 2020 and 203 facilities in 2021 where both GDH and toxin are confirmed by immunochromatography, and CDI is determined when both GDH and toxin are positive/ test is discontinued and CDI is not determined when GDH is positive and toxin is negative. 104 facilities were included in 2020 and 110 facilities in 2021 where both GDH and toxin are confirmed by immunochromatography, and CDI is determined when both GDH and toxin are positive/ toxin is tested by using cultured colony when GDH is positive and toxin us negative, and the test is discontinued when both tested negative. 36 facilities were included in 2020 and 59 facilities in 2021 where both GDH and toxin are confirmed by immunochromatography, and CDI is determined when both GDH and toxin are positive/ toxin is tested by faecal toxin gene testing for GDH-positive and toxin-negative cases, and testing was discontinued in negative cases. 3 facilities were included in 2020 and 1 facility in 2021 where the toxin gene test in faeces alone is used to confirm toxin and determine CDI when positive, and the test is discontinued when negative. 38 other facilities were included in 2020 and 45 other facilities in 2021.

Additional reference

Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE). Annual Report, 2021.

7) Status of health care associated infection

Source: Japan Nosocomial Infections Surveillance (JANIS)

The number of medical institutions participating in the surgical site infection (SSI) division of JANIS has more than doubled over the past 10 years. In 2021 among 291,958 surgical operations undertaken at 768 institutions, SSI were reported in 12,227 cases (4.2%). The number of reported SSI declined from 2011 during the observed period.

In the intensive care unit (ICU) division of JANIS, the incidence of infection by ventilator-associated pneumonia has been 1.2-1.5 per 1,000 days of ICU stay over the past 10 years, with a slightly higher rate of 1.8 per 1,000 days of ICU stay recorded in 2021. Future trends should be monitored. While the incidence of urinary tract infection is around 0.5-0.8 per 1,000 days of ICU stay, the incidence of catheter related bloodstream infection is around 0.6-0.8 per 1,000 days of ICU stay. Both of these rates have been fluctuating slightly. JANIS monitors cases of infections that occurred between 48 hours after admission to ICU and discharge from ICU.

i. Surgical site infection

Table 36. The trend (%) of reported SSI cases

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total SSI cases per total surgical operations (%)*	**6.0**	**6.8**	**6.5**	**6.0**	**5.8**	**5.7**	**5.4**	**5.1**	**4.6**	**4.4**	**4.2**
Participated medical institutions	333	363	442	552	671	730	772	802	785	786	768
Total surgical operations	127,731	129,825	161,077	207,244	251,832	274,132	292,031	305,960	307,052	290,795	291,958
Total SSI cases	7,719	8,771	10,445	12,508	14,701	15,674	15,889	15,566	14,226	12,696	12,227

*Total SSI cases per total surgical operations (%) = (Total SSI cases at medical facilities participated in JANIS) / (Total surgical operations at medical facilities participated in JANIS) times 100

Prepared from annual reports of the SSI division, JANIS.[7]

ii. Infections at Intensive Care Unit (ICU)

Table 37. Incidence rates of infection at ICU

		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Ventilator-ssociated pneumonia	**Total infection incidence rate***	**1.7**	**1.4**	**1.3**	**1.4**	**1.5**	**1.5**	**1.3**	**1.3**	**1.3**	**1.2**	**1.8**
	Total infections at monitored medical institutions	382	327	324	395	522	499	405	409	387	333	508
Urinary tract infection	**Total infection incidence rate***	**0.5**	**0.5**	**0.6**	**0.5**	**0.5**	**0.6**	**0.7**	**0.8**	**0.6**	**0.7**	**0.5**
	Total infections at monitored medical institutions	111	124	143	148	190	219	213	244	174	183	157
Catheter-related bloodstream infection	**Total infection incidence rate***	**0.7**	**0.7**	**0.8**	**0.7**	**0.7**	**0.8**	**0.7**	**0.6**	**0.6**	**0.7**	**0.7**
	Total infections at monitored medical institutions	168	162	204	205	240	263	213	190	177	193	214

*Total infection incidence rate = (Total infections among applicable patients at medial facilities participated in JANIS) / (Total days of ICU stay of applicable patients at medial facilities participated in JANIS) times 1000

Prepared from annual reports of the ICU division, JANIS.[8]

8) Survey of infection treatment and control and the disease burden at hospitals

Source: J-SIPHE, AMR Clinical Reference Center (AMRCRC)

The AMR Clinical Reference Center (AMRCRC) operates the J-SIPHE system, which can be used for AMR measures at hospitals as well as for promoting regional cooperation. The J-SIPHE 2021 Annual Report covers a total of 818 participating medical institutions (547 calculating Infection Prevention and Control Premium 1, 263 calculating Infection Prevention and Control Premium 2, and 8 calculating no premium). Registration information was optional for each participating facility. The median number of blood cultures submitted at hospitals (n=423) was 24.1/1,000 patient days (IQR: 12.8-36.7), while the multiple sets (n=401, counting facilities submitting 20 or more) exceeded 90%. The positive rates (n=401, counting facilities submitting 20 or more) were in the appropriate indicator range, with a median of 14.63 (IRQ: 11.8-18.1). Although the majority of hospitals calculate Premium 1, it is necessary to take into account that there is a range of practices, as Premium 2 also saw an increase in participation

The number of outbreak of bacteria detected in blood samples per 10,000 patient days was the highest for Escherichia coli with a median of 2.21 (IQR: 1.42-3.25), followed by Staphylococcus aureus with 1.53 (IQR: 0.80-2.27), Klebsiella pneumoniae at 0.83 (IQR: 0.36-1.29), showing a slight increase compared to the previous year. On the other hand, the incidence of agent-resistant Staphylococcus aureus, *E. coli*, and *Klebsiella pneumoniae* has remained unchanged. Reinforcement of nosocomial infection control in response to COVID-19 and possible epidemiological changes in inpatients need to be closely monitored together with blood culture submission rates, etc.

The overall hand hygiene compliance rate (n=50) was 68.4%, while the breakdown of the figures by ward function showed that critical care wards (n=321) had the highest rate of compliance, at 75.6%. The total amount of hand rub consumed (n=321) was 10.39 L/1,000 patients overall (IQR: 6.66-16.50), while the breakdown of the figures by ward function showed that critical care wards (n=159) used the most with 52.43 L/1,000 patients (IQR: 28.85-86.57) compared to general wards. The use of hand hygiene products has been on an increasing trend since 2019, indicating an increased awareness of hand hygiene associated with counter measures against COVID-19. Further improvements in hand hygiene practice would be desirable to achieve a hand hygiene compliance target of 70-80%. Furthermore, at facilities with limited infection control human resources are encouraged to monitor infection control over time, using regional cooperation and simple measurement of hand hygiene use as an alternative indicator.

The estimated number of deaths in patients with bloodstream infections was also published after a study of JANIS data carried out with a Health and Labor Sciences Research Grant. The number of deaths due to MRSA has shown declining or unchanged trends, while the number of deaths due to fluoroquinolone-resistant Escherichia coli has remained on the rise and was estimated at 3,915 in 2017. Research into the disease burden of AMR will continue, with the goal of increasing the number of bacterial strains covered over time and ultimately calculating disability-adjusted life years (DALYs). This time, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were added to the list.

DALYs, an indicator of burden of disease that includes losses due to factors other than death (e.g. sequelae), were published. Some of the parameters used in the estimation were borrowed from previous studies overseas, and it is desirable to collect data in Japan for the indices needed for estimation in order to improve the accuracy of burden-of-disease studies in AMR.

Table 38. Basic information on medical institutions participating in J-SIPHE for annual report

	2019	2020	2021
Number of participating facilities	581	778	818
(Premium 1)	(449)	(539)	(547)
(Premium 2)	(127)	(232)	(263)
(without Premium)	(5)	(7)	(8)
Number of beds, median (IQR)	340.5(221.3-525.3)	308.1(196.0-498.3)	301 (184-480)
Average hospital days, median (IQR)	13.6(11.7-17.1)	14.4(12.0-19.0)	14.0 (11.8-19.7)

IQR (Interquartile range)

Table 39. Distribution of multiple sets of blood culture at hospitals (%)

	Median (IQR) 2019	Median (IQR) 2020	Median (IQR) 2021
All patients	90.6(83.6-95.4)(n=276)	92.8(87.9-96.1)(n=326)	93.1(88.0-96.7)(n=401)
Patients aged 15 years and older	95.0(90.8-97.2)(n=276)	95.7(92.3-97.5)(n=326)	96.0(92.8-97.7)(n=401)
Patients aged under 15 years	4.9(0.9-16.8)(n=178)	5.2(0.0-21.7)(n=211)	7.86(1.4-26.7)(n=261)

*Share of submissions of 2 sets or more of blood culture among blood culture submissions

2020: Data from facilities with 20 or more blood culture submissions during the period of interest.

("n" indicates the number of facilities and the distribution of blood culture multiple set rate by hospital)

Table 40. Distribution of occurrences of bloodstream infections at hospitals (total number per 10,000 patient days)

	Median (IQR) 2019(n=253)	Median (IQR) 2020(n=329)	Median (IQR) 2021(n=329)
S. aureus (IQR)*	1.61(0.86-2.17)	1.38(0.75-2.21)	1.53(0.80-2.27)
Enterococcus faecalis (IQR)*	0.37(0.12-0.65)	0.38(0.07-0.65)	0.39(0.12-0.67)
Escherichia coli (IQR)*	2.20(1.40-3.37)	2.13(1.23-3.26)	2.21(1.42-3.25)
Klebsiella pneumoniae (IQR)*	0.83(0.43-1.29)	0.77(0.32-1.26)	0.83(0.36-1.29)
Enterobacter spp. (IQR)*	0.32(0.08-0.61)	0.31(0.00-0.67)	0.34(0.03-0.67)
Streptococcus pneumoniae (IQR)	0(0-0.15)	0(0-0.08)	0(0-0.07)
MRSA (IQR)*	0.59(0.26-0.94)	0.56(0.24-0.89)	0.56(0.26-0.96)
3CREC (IQR)	0.42(0.16-0.84)	0.50(0.14-0.83)	0.49(0.21-0.85)
FQREC (IQR)	0.64(0.27-1.18)	0.66(0.28-1.11)	0.69(0.35-1.13)
3CRKP (IQR)	0(0-0.09)	0(0-0.12)	0(0-0.11)
PRSP (IQR)	0(0-0)	0(0-0)	0(0-0)

MRSA; methicillin resistant *S. aureus*, 3 CREC; 3rd generation Cephalosporine resistant *E. coli*, FQREC; fluoroquinolone resistant *E coli*, 3CRKP; 3rd generation Cephalosporine resistant Klebsiella pneumoniae, PRSP; penicillin resistant *Streptococcus pneumonia*

* The tabulation includes MRSA for *S. aureus*, FQREC or 3CREC for E. coli, 3CRKP for *Klebsiella pneumoniae*, and PRSP for *S. pneumoniae*.

("n" indicates the number of facilities and the distribution of occurrences of bloodstream infections by hospital)

Table 41. Distribution of hand hygiene compliance rate at hospitals (%)

	2019	2020	2021
Overall, median(IQR)	57.5(45.0-68.3) (n=45)	62.6(50.3-75.1) (n=47)	68.4(50.9-78.0) (n=50)
Critical Care Area, median(IQR)	67.0(55.8-75.2) (n=22)	68.9(52.9-78.3) (n=22)	75.6(51.6-83.4) (n=26)
General wards, median(IQR)	56.9(42.6-68.0) (n=44)	62.8(48.4-75.1) (n=41)	67.9(48.4-78.6) (n=48)
Other wards, median(IQR)	59.1(39.0-75.2) (n=22)	68.3(42.6-82.6) (n=26)	64.0(52.0-75.4) (n=26)

("n" indicates the number of facilities and the distribution of hand hygiene compliance rate by hospital)

Table 42. Distribution of total amount of hand sanitizer consumed at hospitals (L/1,000 patient days)

	2019	2020	2021
Overall, median(IQR)	7.41(4.21-11.42) (n=198)	9.63(5.69-14.48) (n=245)	10.39 (6.66-16.50) (n=321)
Critical Care Area, median(IQR)	33.61(18.51-58.52) (n=111)	41.15(28.67-76.19) (n=120)	52.43 (28.85-86.57) (n=159)
General wards, median(IQR)	7.35(4.71-12.16) (n=184)	9.12 (6.36-14.83) (n=219)	9.85 (6.70-15.58) (n=290)
Other wards, median(IQR)	6.31(3.98-12.84) (n=125)	8.95 (4.91-15.57) (n=168)	10.12 (5.71-17.53) (n=227)

("n" indicates the number of facilities and the distribution of total amount of hand sanitizer consumed by hospital)

Table 43. Estimated number of deaths from bloodstream infection (patients)

	2015	2016	2017	2018	2019	2020	2021
S. aureus (95% CI) *	7,372 (5,721-9,047)	7,935 (6,172-9,725)	8,070 (6,271-9,885)	8,187 (6,361-10,034)	8,732 (6,793-10,693)	7,510 (5,399-9,624)	8,039 (5,776-10,316)
MRSA (95% CI)	3,608 (2,357-4,873)	3,758 (2,453-5,078)	3,716 (2,428-5,029)	3,690 (2,411-4,979)	3,966 (2,590-5,363)	3,633 (2,516-4,901)	3,917 (2,715-5,288)
S. pneumoniae (95% CI) *	480 (160-879)	430 (144-787)	447 (149-818)	463 (154-846)	410 (137-750)	247 (82-453)	204 (68-374)
PRSP (95% CI)	126 (42-231)	108 (36-198)	94 (31-173)	113 (38-206)	106 (35-194)	77 (26-141)	74 (25-136)
E. coli (95% CI) *	7,130 (5,701-8,643)	7,636 (6,111-9,251)	8,001 (6,404-9,688)	8,154 (6,523-9,890)	8,666 (6,921-10,506)	8,527 (6,829-10,240)	8,713 (6,983-10,481)
FQREC (95% CI)	2,889 (2,715-3,071)	3,310 (3,113-3,528)	3,376 (3,173-3,591)	3,753 (3,534-3,994)	4,201 (3,955-4,467)	4,118 (3,876-4,394)	4,170 (3,920-4,445)
3CREC (95% CI)	2,146 (1,155-3,300)	2,252 (1,212-3,462)	2,377 (1,280-3,660)	2,647 (1,425-4,074)	3,009 (1,620-4,625)	2,890 (1,559-4245)	3,028 (1,635-4,445)
Klebsiella pneumoniae (95% CI) *	4,167 (3,171-5,276)	4,218 (3,207-5,318)	4,311 (3,275-5,437)	4,561 (3,466-5,755)	4,506 (3,424-5,704)	4,484 (3,405-5,668)	4,529 (3,444-5,727)
3CRKP (95% CI)	474 (344-608)	492 (359-633)	461 (334-592)	533 (386-685)	530 (385-680)	597 (432-761)	682 (495-870)
Pseudomonus aeruginosa (95% CI) *	2,036 (1,320-2,855)	2,109 (1,369-2,957)	2,074 (1,345-2,909)	2,188 (1,418-3,069)	2,243 (1,455-3,148)	2,139 (1,385-2,996)	2,344 (1,516-3,282)
CRPA (95% CI)	343 (296-388)	369 (318-418)	303 (263-343)	318 (275-360)	324 (280-367)	344 (297-388)	399 (345-448)

MRSA; methicillin resistant S. *aureus*, PRSP; penicillin resistant *Streptococcus pneumoniae*, FQREC; fluoroquinolone resistant E. *Coli*, 3CREC; 3rd generation Cephalosporine resistant E. *coli*, 3CRKP; 3rd generation Cephalosporine resistant *Klebsiella pneumoniae*, CRPA; Carbapenem resistant *Pseudomonus aeruginosa*

† The method used to calculate the estimated number of deaths followed that reported by Tsuzuki et al (Tsuzuki S et al. IJID 2021. DOI: 10.1016/j.ijid.2021.05.018). The total number of bacteremia was estimated from the number of beds and the actual number of beds in the number of participating facilities in each year based on JANIS data. This was multiplied by the mortality rate per microorganism obtained from previous studies to arrive at the estimated number of deaths. Mortality from bacteremia by microorganism is listed in the addendum to the following document: https://www.ijidonline.com/article/S1201-9712(21)00419-7/fulltext#supplementaryMaterial.

* *S. aureus* includes MRSA, *S. pneumoniae* includes PRSP, E. *coli* includes FQREC or 3CREC (FQREC and 3CREC are calculated independently for bacteria that are resistant to each drug), *Klebsiella pneumoniae* includes 3CRKP, and *Pseudomonus aeruginosa* includes CRPA.

(): 95% confidence intervals.

9) Survey of infections and antimicrobial use at facilities for the elderly

Source: AMRCRC

Funded by a Health and Labor Sciences Research Grant, the AMRCRC conducted a survey of healthcare-associated infections and antimicrobial use at facilities for the elderly.[9]

i Medical long-term care wards/hospitals

A Point Prevalence Survey (PPS) was conducted by randomly selecting 1,175 facilities with medical long-term care wards from members of the Japan Association of Medical and Care Facilities (January 2020 survey). Eighty facilities (7.8% response rate) responded. The median patient age was 84.0 years (78, 90). The median age of male patients was 82.0 years (75, 87.8) and that of female patients was 87.0 years (80.8, 92). The top infectious foci were pneumonia in 199 patients (39.5%), urinary tract infection in 135 patients (26.8%), and bronchitis in 19 patients (3.8%). The main antimicrobial agents used were injectable third-generation cephalosporins, oral quinolones, carbapenems, and penicillins.

ii Long-term care facilities for the elderly

The center randomly selected facilities from among the members of the Japan Association of Geriatric Health Services Facilities and conducted a PPS. In the 1st PPS (conducted in February 2019, 1,500 facilities), responses were received from 134 facilities (a response rate of 8.9%), in the 2nd PPS (conducted in February 2022, 1,000 facilities), responses were received from 100 facilities (a response rate of 10.0%)

The antimicrobial use rate in the 1st PPS was 1.7% (172 antimicrobial users, total 10,148 residents). The median age of the patients was 86.0 years (IQR: 81-91), while the median age of male patients was 84.0 years (IQR: 75-89) and that of female patients was 87.0 years (IQR: 83-92). The top focus of infection were urinary tract infections, affecting 73 people (47.7%); pneumonia, affecting 31 people (20.3%); and upper respiratory tract infections, affecting 15 people (9.8%). The main antimicrobials used to treat urinary tract infections and pneumonia were fluoroquinolones and third-generation cephalosporins.

The antimicrobial use rate in the 2nd PPS was 1.3% (110 antimicrobial users, total 8,291 residents). The median age of the patients was 89.0 years (IQR: 84-93), while the median age of male patients was 85.0 years (IQR: 80.5-89.5) and that of female patients was 89.0 years (IQR: 86.5-94.0). The top focus of infection were urinary tract infections, affecting 47 people (51.6%); pneumonia, affecting 14 people (15.4%); and cellulitis, affecting 7 people (7.7%). The main antimicrobials used to treat urinary tract infections and pneumonia were oral fluoroquinolones and injectable third-generation cephalosporins.

iii Welfare facilities for the elderly requiring long-term care (special nursing homes for the aged)

The center randomly selected 1,500 welfare facilities for the elderly requiring long-term care from among the members of the Japanese Council of Senior Citizens Welfare Service and conducted a point prevalence survey (PPS). Responses were received from 139 facilities (a response rate of 9.3%). The median age of the patients was 90.0 years (IQR: 85, 93), while the median age of male patients was 80.5 years (IQR: 76, 90) and that of female patients was 92.0 years (IQR: 87, 93).

The top focuses of infection were urinary tract infections, affecting 23 people (31.17%); pneumonia, affecting 11 people (14.9 %); and upper respiratory tract infections, affecting 9 people (12.2%). The main antimicrobials used to treat urinary tract infections were oral quinolones, while the main ones used for pneumonia were injectable third-generation cephalosporins.

Table 44. Use of antimicrobial agents in long-term care wards/hospitals and elderly care facilities

facility ［Number of facilities responding]	Antimicrobial use rate (Antimicrobial users/residents on survey date)	Major infections for which antimicrobial agents were used	Major antimicrobial classes (All infectious diseases)
Medical long-term care (Medical institutions) [82]	9.4% (630/6,729)	Pneumonia (39.5%) Urinary tract infections (26.8%) Bronchitis (3.8%)	Injectable 3rd gen cephalosporins oral fluoroquinolones carbapenems penicillins
Medical and rehabilitation facilities (Geriatric health care) 1st PPS [126]	1.7% (172/10,148)	Urinary tract infection (51.3%) Pneumonia (24.3%) Upper respiratory tract infections (9.9%)	Third generation cephalosporins fluoroquinolones penicillins
2nd PPS [98]	1.3% (110/8,291)	Urinary tract infection (51.6%) Pneumonia (15.4%) Cellulitis (7.7%)	Injectable 3rd gen cephalosporins oral fluoroquinolones penicillins
Nursing care and welfare (Special nursing homes) [137]	1.0% (94/9,044)	Urinary tract infection (31.1%) Pneumonia (14.9%) Upper respiratory tract infection (12.2%)	Injectable 3rd generation cephalosporins oral fluoroquinolones Oral penicillins

(2) Animals

1) Bacteria derived from food-producing animals

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Under the JVARM, antimicrobial susceptibility tests are performed using the broth microdilution method according to the CLSI guidelines. For agents with a breakpoints (BP) established by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents used EUCAST values or were determined microbiologically (midpoint of a bimodal MIC distribution). Agents for which BPs could not be established using these methods were not listed in the table as it was not possible to calculate the resistance rate.

Bacteria derived from diseased animals

Surveys of bacteria derived from diseased animals were carried out using bacteria isolated from food- producing animals which were subjected to pathological appraisal by prefectural livestock hygiene service centers. With regard to the site of bacterial isolation, *Salmonella* spp. were mainly isolated from faeces, gastrointestinal tract and liver, *Staphylococcus* spp. mainly from milk and udder, and *Escherichia coli* mainly from faeces, gastrointestinal tract and lungs.

i. *Salmonella* spp.

Monitoring of antimicrobial resistance was carried out on 11 agents between 2011 and 2018, and on 12 agents in 2019 and 2020 with meropenem (MEPM) added. For resistance rates in cattle- and swine-derived strains collected in 2020, more than 40% were resistant to tetracycline (TC). In contrast, resistance rates in cattle- and swine-derived strains to cefotaxime (CTX) or ciprofloxacin (CPFX), important antibacterial agents in human medicine, were less than 2%, and to MEPM) was 0.0%. It must be noted that the BPs of cefazolin (CEZ), colistin (CL), or CPFX have been lowered since 2016 to bring them into line with the CLSI revisions. The most common *Salmonella* serotypes isolated from diseased food-producing animals from 2014 to 2020 were *S*. Typhimurium and its monophasic variant *S*. 4:i:- among cattle; *S*. Typhimurium, *S*. Choleraesuis, and *S*. 4:i:-among swine; and *S*. Schwarzengrund, *S*. Infantis, and *S*. Enteritidis among chickens. Regarding resistance rates by serotype, more than 50% of *S*. Choleraesuis from swine were resistant to Ampicilline ABPC, TC, or fixed-dose Sulfamethoxazole/trimethoprim (ST). A resistance rate of over 70% was observed to ABPC or TC in S. 4:i:- from cattle and swine, TC in S. Choleraesuis from swaine and S. Infantis from chickens, kanamycin (KM),TC or ST in S. Schwarzengrund from chickens

On the other hand, the resistance rates to CTX or CPFX, important antimicrobial agents in human medicine, were less than 4% for both serotypes.

Table 45. The proportion (%) of antimicrobial-resistant *Salmonella* spp. isolated from diseased animals

Agent	BP	Animal species	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ABPC	32*	Cattle	28.0	32.9	60.7	61.9	56.6	50.0	40.7	36.8	56.1	39.2
		Swine	25.4	25.3	45.0	41.4	46.9	41.1	40.9	50.0	50.7	38.5
		Chickens	12.0	9.4	4.0	3.9	14.3	-	-	4.5	18.8	0.0
CEZ	32 (8* since 2016)	Cattle	10.0	1.2	8.9	7.9	7.9	22.9	5.1	3.5	19.3	19.6
		Swine	0.0	0.0	0.0	0.0	6.1	23.2	6.8	9.4	18.8	13.5
		Chickens	0.0	3.1	4.0	0.0	0.0	-	-	0.0	0.0	0.0
CTX	4*	Cattle	10.0	1.2	8.9	7.9	7.9	4.3	1.7	0.0	1.8	0.0
		Swine	0.0	0.0	0.0	0.0	4.1	0.0	0.0	0.0	0.0	1.9
		Chickens	0.0	0.0	4.0	0.0	0.0	-	-	0.0	0.0	0.0
MEPM	4*	Cattle	-	-	-	-	-	-	-	-	0.0	0.0
		Swine	-	-	-	-	-	-	-	-	0.0	0.0
		Chickens	-	-	-	-	-	-	-	-	0.0	0.0
GM	16*	Cattle	0.0	0.0	0.0	3.2	7.9	4.3	1.7	1.8	1.8	17.6
		Swine	6.3	3.6	15.0	15.5	8.2	17.9	15.9	4.7	7.2	15.4
		Chickens	0.0	0.0	2.0	0.0	0.0	-	-	0.0	18.8	0.0
KM	64*	Cattle	12.0	3.7	25.0	14.3	21.1	25.7	5.1	0.0	8.8	3.9
		Swine	9.5	12.0	6.7	8.6	6.1	10.7	13.6	4.7	18.8	13.5
		Chickens	24.0	15.6	22.0	29.4	42.9	-	-	63.6	62.5	37.5
TC	16*	Cattle	30.0	32.9	66.1	50.8	55.3	42.9	39.0	33.3	56.1	43.1
		Swine	61.9	53.0	66.7	60.3	61.2	58.9	50.0	50.0	44.9	44.2
		Chickens	36.0	34.4	30.0	39.2	42.9	-	-	77.3	68.8	81.3
NA	32*	Cattle	2.0	7.3	1.8	3.2	11.8	5.7	5.1	1.8	1.8	25.5
		Swine	15.9	21.7	5.0	15.5	6.1	7.1	9.1	20.3	24.6	19.2
		Chickens	8.0	6.3	8.0	3.9	28.6	-	-	0.0	43.8	37.5
CPFX	4 (1* since 2016)	Cattle	0.0	0.0	0.0	0.0	0.0	0.0	1.7	1.8	1.8	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	3.6	4.5	4.7	1.4	0.0
		Chickens	0.0	0.0	0.0	0.0	0.0	-	-	0.0	18.8	0.0
CL	16 (4* since 2016)	Cattle	0.0	0.0	0.0	0.0	0.0	1.4	5.1	0.0	1.8	0.0
		Swine	0.0	0.0	1.7	0.0	0.0	3.6	4.5	6.3	8.7	3.8
		Chickens	0.0	3.1	2.0	0.0	0.0	-	-	18.2	18.8	6.3
CP	32*	Cattle	14.0	12.2	10.7	17.5	22.4	12.9	3.4	3.5	28.1	2.0
		Swine	12.7	13.3	11.7	25.9	12.2	8.9	18.2	21.9	10.1	17.3
		Chickens	0.0	6.3	6.0	3.9	14.3	-	-	0.0	0.0	0.0
ST (TMP from 2012 to 2016)	76/4* (TMP is 16*)	Cattle	2.0	1.2	1.8	6.3	13.2	4.3	3.4	1.8	24.6	3.9
		Swine	25.4	21.7	36.7	32.8	22.4	21.4	25.0	12.5	24.6	21.2
		Chickens	20.0	15.6	14.0	29.4	42.9	-	-	59.1	50.0	37.5
Number of isolates tested (n)		Cattle	50	82	56	63	76	70	59	57	57	51
		Swine	63	83	60	58	49	56	44	64	69	52
		Chickens	25	32	50	51	7	-	-	22	16	16

The unit of BP is μg/mL. * BP follows CLSI Criteria.

-: Not under surveillance

Table 46. Number of strains of *Salmonella enterica* isolated from diseased food-producing animals by serotype (FY2011-2020)

Serotypes	Cattle	Swine	Chickens	Total	(%)
Typhimurium	175	250	4	429	29.8
4:i:-	186	106	0	292	20.3
Choleraesuis	3	118	2	123	8.5
Schwarzengrund	6	3	56	65	4.5
Derby	2	29	0	31	2.2
Infantis	19	12	41	72	5.0
Braenderup	7	1	11	19	1.3
Newport	18	7	5	30	2.1
Mbandaka	11	1	12	24	1.7
Thompson	23	2	7	32	2.2
Enteritidis	2	0	15	17	1.2
Dublin	9	0	0	9	0.6
Rissen	19	14	0	33	2.3
Stanley	22	3	0	25	1.7
Tennessee	0	0	8	8	0.6
Others	119	52	59	230	16.0
Total	621	598	220	1439	100

Table 47. Resistance rates (%) of *Salmonella enterica* from diseased animals by serotype (2011-2020)

		Typhimurium		4:i:-		Choleraesuis	Infantis	Schwarzengrund
Agents	BP	Cattle (n=175)	Swine (n=250)	Cattle (n=186)	Swine (n=106)	Swine (n=118)	Chickens (n=41)	Chickens (n=56)
ABPC	32*	49.7	26.8	92.5	70.8	54.2	4.9	3.6
CEZ	8*	13.1	9.6	18.3	17.0	10.2	0.0	0.0
CTX	4*	3.4	0.0	2.7	0.0	1.7	0.0	0.0
GM	16*	1.1	4.4	9.1	12.3	27.1	0.0	0.0
KM	64*	30.3	4.4	6.5	4.7	33.1	46.3	76.8
TC	16*	41.7	40.8	90.3	84.0	75.4	75.6	94.6
NA	32*	6.3	10.0	9.7	13.2	33.9	12.2	21.4
CPFX	1*	0.0	3.2	1.1	1.9	3.4	0.0	0.0
CL	4*	0.6	5.2	2.7	5.7	0.0	4.9	3.6
CP	32*	18.3	22.0	12.9	12.3	11.9	2.4	3.6
ST (TMP from 2012 to 2016)	76/4* (TMP is 16*)	3.4	20.4	10.8	6.6	54.2	43.9	69.6

The unit of BP is μg/mL.* BP follows CLSI Criteria. ** TMP from 2012 to 2016

ii. *Staphylococcus aureus*

Monitoring of antimicrobial resistance was carried out on 7 agents between 2011 and 2018 and on 8 agents in 2019 and 2020 with Oxacillin (MPIPC) added. Resistance rates of ABPC and tetracycline (TC) in swine-derived strains were observed to exceed 50% in 2020. Resistance rates to all antimicrobials were observed to be higher in strains isolated from swine than in those derived from cattle and chickens. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was less than 1% in strains isolated from cattle, while it was 23.8% in strains from swine, and 16.7% in strains from chickens.

Table 48. Resistance rates (%) of *Staphylococcus aureus* isolated from disease appraisal samples

Agents*.	BP	Animal species	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ABPC (PCG since 2019)	0.5	Cattle	5.5	13.6	11.0	11.1	21.3	7.8	7.4	8.1	6.4	4.7
		Swine	-	-	-	-	-	75.6	71.4	82.4	87.5	81.0
		Chickens	0.0	25.0	0.0	15.4	50.0	3.7	22.6	8.0	0.0	12.5
MPIPC	4†	Cattle	-	-	-	-	-	-	-	-	2.4	0.8
		Swine	-	-	-	-	-	-	-	-	15.0	4.8
		Chickens	-	-	-	-	-	-	-	-	0.0	0.0
SM	64	Cattle	6.4	2.3	2.8	1.1	2.7	1.4	3.4	5.8	8.0	3.1
		Swine	-	-	-	-	-	33.3	20.4	39.2	17.5	19.0
		Chickens	0.0	10.0	0.0	7.7	16.7	3.7	0.0	0.0	0.0	0.0
GM	16†	Cattle	0.9	2.3	1.8	0.0	1.3	0.0	0.6	0.0	0.0	0.8
		Swine	-	-	-	-	-	2.2	14.3	11.8	7.5	4.8
		Chickens	0.0	15.0	0.0	0.0	0.0	3.7	9.7	4.0	0.0	0.0
EM	8†	Cattle	1.8	3.4	5.5	0.0	6.7	2.8	1.7	6.4	4.8	3.9
		Swine	-	-	-	-	-	37.8	38.8	52.9	52.5	33.3
		Chickens	50.0	55.0	0.0	15.4	16.7	22.2	6.5	4.0	17.6	4.2
TC	16†	Cattle	0.0	2.3	8.3	5.5	6.7	0.0	0.0	0.6	2.4	0.8
		Swine	-	-	-	-	-	57.8	53.1	60.8	77.5	52.4
		Chickens	37.5	5.0	0.0	16.7	16.7	33.3	19.4	20.0	17.6	20.8
CP	32†	Cattle	0.0	0.0	0.9	0.0	1.3	0.0	0.6	0.6	1.6	0.0
		Swine	-	-	-	-	-	22.2	30.6	43.1	37.5	23.8
		Chickens	0.0	0.0	0.0	15.4	33.3	3.7	3.2	8.0	0.0	12.5
CPFX	4†	Cattle	0.0	0.0	0.9	0.0	1.3	0.7	0.6	0.0	1.6	0.8
		Swine	-	-	-	-	-	11.1	8.2	23.5	5.0	23.8
		Chickens	25.0	0.0	4.2	15.4	33.3	3.7	3.2	28.0	0.0	16.7
Number of isolates tested (n)		Cattle	109	88	109	91	75	141	175	172	125	128
		Swine	-	-	-	-	-	45	49	51	40	21
		Chickens	8	20	24	12	6	27	31	25	17	24

Units of BP are in μg/ml. -: Swine-derived strains up to 2015 are not shown because the number of isolates was less than 5 in each year.

* NA is also included in the survey, but its resistance rates are not listed as BPs cannot be set. † BP follows CLSI Criteria.

iii. *Escherichia coli*

Monitoring of antimicrobial resistance was carried out on 12 agents between 2012 and 2018 and on 13 agents in 2019 and 2020. In 2020, an antimicrobial resistance rate exceeding 50% was observed to ABPV, SM and TC in cattle-, swine- and chicken-derived isolates and to chloramphenicol (CP) or ST in swine-derived isolates. Resistance rates to 6 out of 13 antimicrobials were observed to be higher in strains isolated from cattle than in those derived from swine and chickens. Resistance to CTX, CPFX, and CL, which are critically important antimicrobials for human medicine, was in the ranges 2.4 to 22.3%, 18.9 to 28.7%, and 0.0 to 27.1%, respectively, while the resistance rate to MEPM was 0.0%. It must be noted that the BPs of CEZ and CL since 2016 and CPFX since 2019 are the CLSI's revised figures. For CL, in 2018 it was positioned as a second-line agent for veterinary use and as a feed additive its designation was revoked and its use was prohibited. The resistance rate to CL showed more than 50% for swine-derived strains in 2017, but it decreased to 27.1% in 2020, and it will be necessary to continue to monitor future trends in the resistance rate due to the strengthening of these risk management measures.

Table 49. Resistance rates (%) of *Escherichia coli* isolated from disease appraisal material

Agent	BP	Animal species	2012†	2013†	2014†	2015	2016	2017	2018	2019	2020
ABPC	32*	Cattle	-	61.4	57.8	63.8	37.7	50.0	51.7	62.8	63.8
		Swine	-	65.2	50.4	57.4	74.5	70.7	62.8	68.3	61.2
		Chickens	75.6	54.2	-	60.4	43.5	33.3	52.9	47.5	56.8
CEZ	8* (32 before 2015)	Cattle	-	21.1	6.7	14.9	15.6	15.6	17.2	28.7	27.7
		Swine	-	10.1	6.1	9.3	34.3	35.0	21.5	23.8	17.6
		Chickens	40.2	16.7	-	14.6	15.2	11.1	17.6	20.0	13.5
CTX	4*	Cattle	-	10.5	6.7	8.5	7.8	8.9	9.2	14.9	22.3
		Swine	-	2.5	0.0	3.7	2.9	3.3	3.3	5.0	2.4
		Chickens	37.8	14.6	-	10.4	6.5	5.6	11.8	7.5	8.1
SM	32	Cattle	-	-	68.9	78.7	49.4	61.1	57.5	63.8	63.8
		Swine	-	-	64.3	66.7	74.5	72.4	54.5	65.3	61.2
		Chickens	-	-	-	60.4	56.5	38.9	51.0	65.0	67.6
GM	16*	Cattle	-	17.5	6.7	12.8	10.4	8.9	10.3	8.5	11.7
		Swine	-	24.1	8.7	19.4	21.6	22.8	13.2	12.9	14.1
		Chickens	6.1	3.1	-	2.1	10.9	5.6	2.0	5.0	10.8
KM	64*	Cattle	-	38.6	26.7	29.8	16.9	26.7	28.7	31.9	29.8
		Swine	-	34.2	33.9	31.5	46.1	39.0	32.2	27.7	24.7
		Chickens	51.2	35.4	-	39.6	50.0	36.1	27.5	25.0	37.8
TC	16*	Cattle	-	50.9	66.7	66.0	54.5	62.2	58.6	66.0	66.0
		Swine	-	79.1	75.7	75.9	87.3	78.9	70.2	69.3	69.4
		Chickens	74.4	61.5	-	70.8	78.3	55.6	72.5	60.0	70.3
MEPM	4*	Cattle	-	-	-	-	-	-	-	0.0	0.0
		Swine	-	-	-	-	-	-	-	0.0	0.0
		Chickens	-	-	-	-	-	-	-	0.0	0.0
NA	32*	Cattle	-	29.8	33.3	36.2	18.2	33.3	33.3	36.2	34.0
		Swine	-	60.1	52.2	50.0	48.0	50.4	33.1	27.7	32.9
		Chickens	73.2	59.4	-	52.1	56.5	55.6	35.3	60.0	32.4
CPFX	4* (1 since 2019)	Cattle	-	19.3	24.4	34.0	11.7	17.8	21.8	28.7	28.7
		Swine	-	36.1	23.5	32.4	24.5	28.5	22.3	15.8	20.0
		Chickens	22.0	25.0	-	8.3	8.7	11.1	11.8	35.0 §1	18.9
CL	4* (16 before 2015)	Cattle	-	5.3	6.7	0.0	10.4	20.0	11.5	11.7	1.1
		Swine	-	3.2 §2	0.0 §2	2.8 §2	56.9	52.0	35.5	27.7	27.1
		Chickens	2.4	1.0	-	0.0	8.7	0.0	2.0	10.0	0.0
CP	32*	Cattle	-	21.1	28.9	46.8	19.5	28.9	31.0	38.3	40.4
		Swine	-	64.6	64.3	61.1	69.6	59.3	57.0	55.4	57.6
		Chickens	22.0	25.0	-	16.7	21.7	11.1	21.6	15.0	32.4
ST (TMP from 2012 to 2017)	ST is 76/4* (TMP is 16*)	Cattle	-	22.8	33.3	44.7	23.4	35.6	42.5	41.5	40.4
		Swine	-	49.4	59.1	64.8	62.7	56.9	52.9	57.4	51.8
		Chickens	31.7	33.3	-	33.3	23.9	13.9	19.6	35.0	24.3
Strains tested (n)		Cattle	-	57	45	47	77	90	87	94	94
		Swine	-	158	108	108	102	123	121	101	85
		Chickens	82	96	-	48	46	36	51	40	37

The unit of BP is μg/mL. * BP follows CLSI Criteria. †-: Not under surveillance.

§1 The resistance rate to CPFX in chicken-derived strains for 2019 was 22.5% when adopting the pre-2018 BP:4.

§2 The resistance rates to CL in swine-derived strains for 2013, 2014, and 2015 were 42.4%, 44.3%, and 62.0%, respectively, when adopting the post-2016 BP:4.

Bacteria derived from healthy food-producing animals

Surveillance of food-borne pathogenic bacteria and indicator bacteria from healthy food-producing animals was carried out using samples of feces collected at animal and poultry slaughterhouses. When JVARM first began, surveillance was carried out using samples of feces from food-producing animals collected at farms by livestock hygiene service centers. Surveillance at animal and poultry slaughterhouses was parallelly launched in FY2012, as this facilitated more intensive sampling at a stage closer to the final food product. In FY2016, there was confirmed to be no major difference in the findings of both surveys, so JVARM shifted to surveillance at animal and poultry slaughterhouses for bacteria derived from healthy food-producing animals.

i. *Escherichia coli*

Monitoring of antimicrobial resistance on 12 agents between 2012 and 2017, and 13 agents adding MEPM since 2018 was carried out. In 2020, resistance to SM and TC in swine- and chicken-derived strains ABPC in swine-derived strain and nalidixic acid (NA) in chicken-derived strains was observed to exceed 40%. The rates of resistance to critically important antimicrobials for human medicine CTX, CPFX, and CL were less than 5% less than 15%, and less than 5%, respectively, while the resistance rate to MEPM was 0.0%.

Table 50. Resistance rates (%) of *Escherichia coli* from animal slaughterhouses and poultry slaughterhouses

Agent	BP	Animal species	2012	2013	2014	2015	2016	2017	2018	2019	2020
ABPC	32*	Cattle	2.4	6.5	3.0	5.5	7.4	4.8	11.6	6.3	5.1
		Swine	32.3	26.0	43.0	34.4	36.7	33.7	34.9	32.5	44.1
		Chickens	30.8	35.5	40.1	43.5	35.4	39.3	36.1	36.7	30.6
CEZ	8* (32 before 2015)	Cattle	0.4	0.3	0.0	0.0	1.9	0.8	0.5	1.0	0.4
		Swine	1.0	0.8	1.1	1.0	6.7	1.2	2.4	3.8	1.1
		Chickens	3.0	7.8	5.8	3.8	10.1 §1	6.7 §1	7.7 §1	4.7 §1	6.6
CTX	4*	Cattle	0.0	0.0	0.4	0.0	0.4	0.4	0.0	0.7	0.0
		Swine	0.0	0.0	1.1	0.0	1.1	1.2	0.0	2.5	0.0
		Chickens	1.5	4.8	4.1	2.2	5.1	4.7	3.2	3.1	4.1
MEPM	4*	Cattle	—	—	—	—	—	—	0.0	0.0	0.0
		Swine	—	—	—	—	—	—	0.0	0.0	0.0
		Chickens	—	—	—	—	—	—	0.0	0.0	0.0
SM	32	Cattle	14.9	12.3	17.1	12.4	22.1	19.0	18.5	19.7	14.6
		Swine	44.1	44.9	52.7	39.6	50.0	41.0	49.4	41.3	45.2
		Chickens	39.1	38.6	44.8	41.8	51.3	41.3	48.4	40.6	47.1
GM	16*	Cattle	0.0	0.3	0.0	0.0	0.8	0.0	0.0	0.0	0.4
		Swine	0.5	2.4	6.5	2.1	3.3	3.6	3.6	2.5	1.1
		Chickens	1.5	1.8	2.9	2.2	5.1	6.0	5.2	6.3	3.3
KM	64*	Cattle	1.2	1.5	0.4	0.7	4.3	1.2	0.0	0.7	0.4
		Swine	9.7	7.9	9.7	8.3	10.0	10.8	8.4	10.0	5.4
		Chickens	24.1	24.1	33.1	37.5	43.0	36.7	43.9	37.5	31.4
TC	16*	Cattle	19.0	16.4	19.8	18.6	29.8	21.0	26.5	22.9	19.8
		Swine	58.5	62.2	59.1	45.8	56.7	55.4	55.4	47.5	62.4
		Chickens	49.6	44.0	43.6	54.9	56.3	46.0	49.0	62.5	52.9
NA	32*	Cattle	2.4	1.8	2.3	2.6	2.3	2.0	2.1	1.4	3.2
		Swine	4.1	11.0	9.7	5.2	15.6	12.0	12.0	11.3	8.6
		Chickens	39.8	36.1	45.3	35.9	35.4	39.3	40.6	36.7	48.8
CPFX	4*	Cattle	0.0	0.6	0.8	0.0	0.4	0.0	0.5	0.3	0.4
		Swine	1.5	0.8	2.2	3.1	4.4	0.0	1.2	2.5	1.1
		Chickens	6.0	5.4	9.9	4.9	9.5	12.0	12.3	12.5	14.0
CL	4* (16 before 2015)	Cattle	0.0	0.0	0.8	0.0	0.4	1.2	0.0	0.3	0.0
		Swine	0.0	0.0	0.0	0.0	4.4 §2	2.4 §2	6.0 §2	2.5 §2	4.3
		Chickens	0.8	0.6	0.0	0.5	1.9	3.3	0.0	0.0	0.8
CP	32*	Cattle	5.2	2.3	3.8	2.9	2.3	2.8	4.8	4.2	5.9
		Swine	23.6	23.6	34.4	25.0	25.6	21.7	25.3	22.5	30.1
		Chickens	11.3	11.4	15.1	9.8	19.6	11.3	17.4	15.6	20.7
ST	76/4*	Cattle	2.0	2.9	5.3	2.9	0.4	2.0	5.3	2.8	2.8
		Swine	23.6	26.8	34.4	30.2	4.4	26.5	32.5	23.8	25.8
		Chickens	24.8	31.9	30.2	28.3	27.8	34.7	33.5	30.5	22.3
Number of isolates tested (n)		Cattle	248	341	263	274	258	252	189	288	253
		Swine	195	127	93	96	90	83	83	80	93
		Chickens	133	166	172	184	158	150	155	128	121

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

§1 If the BP of 32 used until 2015 is applied, CEZ resistance rate in chicken-derived strains was 7.0% in 2016, 4.7% in 2017, 3.2% in 2018, and 3.5% in 2019.

§2 If the BP of 16 used until 2015 is applied, CL resistance rate in swine-derived strains was 1.1% in 2016, 0.0% in 2017, 0.0% in 2018, and 0.0% in 2019.

ii. *Campylobacter jejuni*

Monitoring of antimicrobial resistance on 7 agents between 2012 and 2016, and 8 agents adding azithromycin (AZM) since 2017 was carried out. In 2020, resistance to TC, NA, and CPFX in cattle- and chicken-derived strains and TC in cattle-derived strain exceeded 30%. On the other hand, resistance to SM, EM, and CP were all less than 5%. Resistance to CPFX and AZM, which are a critically important antimicrobials for human medicine, were 62.7% and 2.7% in cattle-derived strains, respectively, and 32.7% and 4.1% in chicken-derived strains, respectively.

Table 51. Resistance rates (%) of *Campylobacter jejuni* from animal and poultry slaughterhouses

Agents*	BP	Animal species	2012	2013	2014	2015	2016	2017	2018	2019	2020
ABPC	32	Cattle	0.0	9.1	12.9	8.9	7.4	8.2	8.6	11.1	8.2
		Chickens	19.7	19.8	17.5	19.1	16.2	28.4	14.9	14.3	22.4
SM	16	Cattle	2.4	3.5	3.8	3.2	6.2	4.1	5.7	1.7	3.6
		Chickens	1.4	0.0	3.5	2.1	8.8	1.5	0.0	0.0	2.0
EM	32†	Cattle	0.0	0.7	0.0	1.3	0.0	0.0	2.9	0.9	2.7
		Chickens	0.0	0.0	0.0	0.0	0.0	1.5	0.0	0.0	4.1
AZM	4	Cattle	—	—	—	—	—	0.0	2.9	0.9	2.7
		Chickens	—	—	—	—	—	1.5	0.0	0.0	4.1
TC	16†	Cattle	45.1	52.4	49.2	52.2	63.0	72.2	62.9	68.4	70.9
		Chickens	38.0	44.4	38.6	28.7	33.8	46.3	23.4	34.3	22.4
CP	16	Cattle	0.0	6.3	0.0	1.3	1.2	6.2	2.9	6.8	0.9
		Chickens	0.0	0.0	1.8	0.0	2.9	0.0	2.1	0.0	0.0
NA	16	Cattle	34.1	33.6	50.8	42.7	44.4	48.5	31.4	60.7	62.7
		Chickens	39.4	48.1	29.8	27.7	57.4	46.3	31.9	37.1	32.7
CPFX	4†	Cattle	34.1	29.4	49.2	40.8	44.4	50.5	31.4	59.8	62.7
		Chickens	39.4	39.5	29.8	26.6	51.5	44.8	29.8	34.3	32.7
Strains tested (n)		Cattle	82	143	132	157	81	97	35	117	110
		Chickens	71	81	57	94	68	67	47	35	49

The unit of BP is μg/mL.

While GM were also included in the scope of monitoring, the proportion of GM-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

iii. *Campylobacter coli*

Monitoring of antimicrobial resistance to 7 agents between 2012 and 2016 was carried out, and AZM was added in 2017, taking the total number to 8. In swine-derived strains in 2020, resistance to SM or TC exceeding 70%, and resistance to NA or CPFX exceeding 50% was observed. On the other hand, CP resistance was less than 3%. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 50.0%, while the AZM resistance rate was 21.4%.

Table 52. Resistance rates (%) of slaughterhouse-derived *Campylobacter coli*

Agent*	BP	Animal species	2012	2013	2014	2015	2016	2017	2018	2019	2020
ABPC	32	Swine	23.3	25.5	36.6	24.6	15.4	29.5	17.2	26.7	21.4
SM	32	Swine	67.4	78.3	69.9	72.3	64.1	68.9	69.0	68.3	71.4
EM	32†	Swine	32.6	44.3	43.0	26.2	38.5	31.1	20.7	33.3	21.4
AZM	4	Swine	—	—	—	—	—	31.1	20.7	31.7	21.4
TC	16†	Swine	84.5	93.4	80.6	87.7	89.7	83.6	86.2	78.3	73.8
CP	16	Swine	10.9	3.8	7.5	9.2	15.4	1.6	3.4	3.3	2.4
NA	32	Swine	46.5	53.8	52.7	47.7	61.5	50.8	58.6	45.0	52.4
CPFX	4†	Swine	46.5	46.2	50.5	47.7	59.0	54.1	58.6	40.0	50.0
Strains tested (n)		Swine	129	106	93	65	39	61	29	60	42

The unit of BP is μg/mL.

* While GM was also included in the scope of monitoring, the proportion of GM-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

iv. *Enterococcus* spp.

Monitoring of antimicrobial resistance was carried out on 10 agents between 2012 and 2014, and 11 agents since 2015 vancomycin（VCM) added. From 2018, dihydrostreptomycin (DSM), oxytetracycline (OTC) and enrofloxacin (ERFX) were changed to SM, TC and CPFX, respectively, of which resistance rates were investigated for 10 agents excepting SM as no BPs were established for it. In 2020, resistance rates exceeding 40% were observed to lincomycin (LCM) or KM in chicken-derived strains and to TC in swine- and chicken-derived strains. In contrast, resistance rates to ABPC were less than 1% in all cattle-, swine-, and chicken-derived strains. Resistance rates to CPFX, which belongs to the fluoroquinolone class of antibiotics important in human medicine, ranged from 0.0 to 7.3%. The resistance rate to VCM, which is important in human medicine, was 0.0%.

In 2020, among *Enterococcus* spp., *E. faecalis* ranged from 7.9% of cattle-derived strains (21 out of 267) to 44.6% of chicken-derived strains (86 out of 193), and *E. faecium* ranged from 1.9% of cattle-derived strains (5 out of 267) to 11.4% of chicken-derived strains (22 out of 193). Resistance to CPFX —one of the fluoroquinolones, which are critically important antimicrobials for human medicine—in *E. faecalis* derived from cattle- and chicken-derived strains were 0.0% and 5.1% respectively, and in *E. faecium* derived from swine and chicken were 28.6% and 36.4% of, respectively, with higher rates observed in *E. faecium* from swine and chicken.

Table 53. Resistance rates (%) of *Enterococcus* spp. from animal slaughterhouses

Agent*	BP	Animal species	2012	2014 †	2015	2016	2017	2018	2019	2020
ABPC	16 §	Cattle	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	0.0	0.6	0.0	0.0	0.0	0.0	0.8	0.5
DSM	128	Cattle	85.6	31.2	14.9	2.9	0.8	-	-	-
		Swine	82.0	55.7	34.4	29.7	28.0	-	-	-
		Chickens	69.2	30.9	49.2	30.6	27.0	-	-	-
GM	32	Cattle	61.2	4.2	2.2	0.8	0.0	13.5	3.1	7.5
		Swine	43.3	3.4	3.1	4.4	1.2	19.0	10.0	6.5
		Chickens	29.3	5.5	9.4	4.5	3.4	12.6	9.5	6.2
KM	128	Cattle	55.2	5.0	4.1	1.3	0.8	15.9	6.3	13.9
		Swine	56.2	20.5	31.3	17.6	22.0	35.4	21.3	33.1
		Chickens	68.4	37.0	47.0	41.4	41.9	61.6	49.2	48.2
OTC	16	Cattle	24.4	21.2	27.1	27.6	26.4	-	-	-
		Swine	61.9	54.5	59.4	64.8	58.5	-	-	-
		Chickens	72.2	58.0	63.0	66.2	52.0	-	-	-
TC	16 §	Cattle	-	-	-	-	-	24.7	24.3	28.5
		Swine	-	-	-	-	-	58.2	55.0	66.9
		Chickens	-	-	-	-	-	64.2	54.8	63.2
CP	32 §	Cattle	1.5	0.0	0.0	0.4	0.4	0.6	0.4	0.4
		Swine	17.5	17.0	10.4	15.4	14.6	15.2	11.3	16.1
		Chickens	13.5	8.8	7.2	10.2	8.8	9.3	12.7	9.8
EM	8 §	Cattle	5.0	3.8	1.5	2.5	2.1	1.8	2.4	4.9
		Swine	41.8	28.4	30.2	34.1	26.8	27.8	23.8	31.5
		Chickens	50.4	43.1	42.5	45.2	41.2	36.4	34.9	36.8
LCM	128	Cattle	27.9	3.1	0.7	2.5	2.1	1.8	2.0	3.4
		Swine	59.8	50.0	34.4	37.4	35.4	36.7	41.3	39.5
		Chickens	52.6	34.3	43.1	47.1	40.5	37.7	41.3	40.9
ERFX	4	Cattle	6.0	1.2	0.4	0.8	0.0	-	-	-
		Swine	22.7	9.1	2.1	1.1	3.7	-	-	-
		Chickens	9.8	3.9	13.3	3.8	2.7	-	-	-
CPFX	4 §	Cattle	-	-	-	-	-	2.4	1.6	0.0
		Swine	-	-	-	-	-	17.7	7.5	4.8
		Chickens	-	-	-	-	-	6.6	11.1	7.3
TS.	64	Cattle	2.0	2.3	0.7	2.1	2.5	1.8	2.4	3.4
		Swine	33.0	21.6	19.8	28.6	24.4	26.6	23.8	29.8
		Chickens	49.6	42.0	35.9	42.7	41.2	34.4	34.1	30.6
VCM	32	Cattle	-	-	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	-	-	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	-	-	0.0	0.0	0.0	0.0	0.0	0.0
Number of isolates tested (n)		Cattle	201	260	269	289	242	170	255	267
		Swine	194	88	96	91	82	79	80	124
		Chickens	133	181	181	157	148	151	126	193

The unit of BP is μg/mL.

* While AZM, SM, NA, BC and SNM were also included in the scope of the survey, the resistance rates were not listed because BP could not be established.

† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in FY2013.

§ BP follows CLSI Criteria.

-: Not under surveillance.

Table 54. Resistance rates (%) of *Enterococcus faecalis* from animal slaughterhouses

Agent*	BP	Animal species	2012	2014 †	2015	2016	2017	2018	2019	2020
ABPC	16 §	Cattle	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0
DSM	128	Cattle	90.6	36.4	35.7	12.5	0.0	-	-	-
		Swine	88.2	62.5	100.0	43.5	38.5	-	-	-
		Chickens	76.9	53.8	72.4	40.6	38.8	-	-	-
GM	32	Cattle	68.8	27.3	0.0	0.0	0.0	40.0	0.0	14.3
		Swine	76.5	12.5	15.4	8.7	7.7	31.0	35.7	17.9
		Chickens	35.6	9.9	14.3	6.3	3.5	15.1	15.0	7.0
KM	128	Cattle	71.9	9.1	14.3	0.0	0.0	46.7	0.0	19.0
		Swine	72.9	12.5	69.2	30.4	30.8	51.7	42.9	53.8
		Chickens	71.2	57.1	66.3	55.2	58.8	66.0	51.7	47.7
OTC	16	Cattle	31.3	27.3	28.6	37.5	10.0	-	-	-
		Swine	64.7	87.5	92.3	73.9	84.6	-	-	-
		Chickens	75.0	67.0	70.4	83.3	65.9	-	-	-
TC	16 §	Cattle	-	-	-	-	-	26.7	25.0	14.3
		Swine	-	-	-	-	-	65.5	57.1	66.7
		Chickens	-	-	-	-	-	70.8	66.7	77.9
CP	32 §	Cattle	9.4	0.0	0.0	12.5	10.0	6.7	25.0	4.8
		Swine	30.6	62.5	53.8	39.1	38.5	27.6	35.7	41.0
		Chickens	17.3	13.2	9.2	15.6	12.9	11.3	20.0	14.0
EM	8 §	Cattle	21.9	9.1	0.0	0.0	10.0	0.0	25.0	9.5
		Swine	51.8	62.5	69.2	52.2	61.5	44.8	50.0	56.4
		Chickens	58.7	64.8	60.2	59.4	58.8	43.4	53.3	44.2
LCM	128	Cattle	34.4	9.1	0.0	0.0	10.0	0.0	25.0	4.8
		Swine	76.5	75.0	92.3	56.5	61.5	51.7	50.0	59.0
		Chickens	57.7	45.1	54.1	59.4	55.3	43.4	55.0	43.0
ERFX	4	Cattle	3.1	0.0	0.0	0.0	0.0	-	-	-
		Swine	5.9	0.0	7.7	0.0	0.0	-	-	-
		Chickens	2.9	1.1	0.0	2.1	0.0	-	-	-
CPFX	4 §	Cattle	-	-	-	-	-	0.0	0.0	0.0
		Swine	-	-	-	-	-	3.4	7.1	5.1
		Chickens	-	-	-	-	-	2.8	3.3	0.0
TS.	64	Cattle	6.3	0.0	0.0	0.0	10.0	0.0	25.0	4.8
		Swine	50.6	62.4	69.2	52.2	61.5	44.8	50.0	56.4
		Chickens	57.7	65.9	53.1	59.4	60.0	43.4	55.0	44.2
VCM	32	Cattle	-	-	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	-	-	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	-	-	0.0	0.0	0.0	0.0	0.0	0.0
Strains tested (n)		Cattle	32	11	14	8	10	15	4	21
		Swine	85	8	13	23	13	29	14	39
		Chickens	104	91	98	96	85	106	60	86

The unit of BP is μg/mL.

* While AZM, SM, NA, BC and SNM were also included in the scope of the survey, the resistance rates were not listed because BP could not be established.

† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in FY2013.

§ BP follows CLSI Criteria.

-: Not under surveillance.

Table 55. Resistance rates (%) of *Enterococcus faecium* from animal slaughterhouses

Agent*	BP	Animal species	2012	2014†	2015	2016	2017	2018	2019	2020
ABPC	16§	Cattle	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0
		Chickens	2.4	0.0	0.0	0.0	0.0	0.0	0.0	4.5
DSM	128	Cattle	22.7	33.3	0.0	25.0	0.0	-	-	-
		Swine	30.3	58.3	0.0	28.6	27.3	-	-	-
		Chickens	28.6	13.9	16.1	30.0	18.2	-	-	-
GM	32	Cattle	2.3	0.0	0.0	0.0	0.0	-	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	50.0	-	0.0
		Chickens	3.6	2.8	3.2	10.0	9.1	0.0	0.0	4.5
KM	128	Cattle	34.1	33.3	16.7	0.0	50.0	-	0.0	20.0
		Swine	30.3	25.0	72.7	28.6	72.7	100.0	-	57.1
		Chickens	34.5	33.3	35.5	40.0	45.5	90.0	85.7	100.0
OTC	16	Cattle	9.1	0.0	16.7	0.0	0.0	-	-	-
		Swine	42.4	41.7	9.1	42.9	54.5	-	-	-
		Chickens	63.1	58.3	64.5	60.0	31.8	-	-	-
TC	16§	Cattle	-	-	-	-	-	-	0.0	0.0
		Swine	-	-	-	-	-	50.0	-	28.6
		Chickens	-	-	-	-	-	60.0	57.1	72.7
CP	32§	Cattle	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0
		Swine	0.0	25.0	0.0	0.0	9.1	0.0	-	0.0
		Chickens	4.8	8.3	6.5	0.0	9.1	10.0	28.6	4.5
EM	8§	Cattle	11.4	0.0	33.3	25.0	0.0	-	0.0	40.0
		Swine	15.2	58.3	54.5	57.1	45.5	0.0	-	14.3
		Chickens	32.1	30.6	35.5	20.0	27.3	40.0	28.6	50.0
LCM	128	Cattle	9.1	0.0	0.0	0.0	0.0	-	0.0	0.0
		Swine	39.4	50.0	9.1	28.6	27.3	0.0	-	14.3
		Chickens	31.0	19.4	29.0	20.0	27.3	20.0	28.6	40.9
ERFX	4	Cattle	36.4	0.0	16.7	25.0	0.0	-	-	-
		Swine	45.5	25.0	0.0	0.0	27.3	-	-	-
		Chickens	65.5	13.9	71.0	30.0	18.2	-	-	-
CPFX	4§	Cattle	-	-	-	-	-	-	0.0	0.0
		Swine	-	-	-	-	-	0.0	-	28.6
		Chickens	-	-	-	-	-	20.0	42.9	36.4
TS.	64	Cattle	9.1	0.0	0.0	0.0	0.0	-	0.0	0.0
		Swine	12.1	16.7	0.0	28.6	18.2	0.0	-	0.0
		Chickens	26.2	19.4	22.6	20.0	27.3	20.0	28.6	18.2
VCM	32	Cattle	-	-	0.0	0.0	0.0	-	0.0	0.0
		Swine	-	-	0.0	0.0	0.0	0.0	-	0.0
		Chickens	-	-	0.0	0.0	0.0	0.0	0.0	0.0
Strains tested (n)		Cattle	44	6	6	4	4	0	1	5
		Swine	84	12	11	7	11	2	0	7
		Chickens	64	36	31	10	22	10	7	22

The unit of BP is μg/mL.

* While AZM, SM, NA, BC and SNM were also included in the scope of the survey, the resistance rates were not listed because BP could not be established.

† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in FY2013.

§ BP follows CLSI Criteria.

-: Not under surveillance.

v. *Salmonella* spp.

Monitoring of 12 agents in chicken-derived strains was carried out between 2012 and 2017, and MEPM was added in 2018, bringing the number monitored to 13 agents. Among chicken-derived strains in 2020 resistance to TC exceeding 70%, resistance to KM exceeding 60%, and resistance to SM or ST exceeding 40% were observed. On the other hand, resistance to ABPC or CEZ was less than 2%, and no resistance to CP or gentamicin (GM) was observed. In the realm of critically important antimicrobials for human medicine, the rate of resistance to CTX and CPFX was less than 1.0%, and resistance to CL or MEPM was 0.0%.

The *Salmonella* serotypes most commonly isolated from poultry slaughterhouses in FY2015-2020 were *S.* Schwarzengrund, *S.* Infantis, and *S.* Typhimurium. In a comparison of *Salmonella* serotypes isolated from poultry slaughterhouses with those isolated from food and from humans (source: Nippon AMR One Health Report 2021: Table 19) (Table 58, Figure 1), the same trends were observed in *Salmonella* serotypes isolated from poultry slaughterhouses as in those isolated from food. The top two serotypes isolated from poultry slaughterhouses were the same as those isolated from food, respectively accounting for 89% and 72% of all serotypes from those sources, which suggested a relationship between them. On the other hand, the serotypes isolated from humans were more diverse than those isolated from poultry slaughterhouses and food, with the top two serotypes isolated from poultry slaughterhouses accounting for 15% of human-derived strains, which suggested the possibility that there are variety of origin other than poultry or their food products. In a comparison of resistance rates between *S.* Schwarzengrund and *S.* Infantis, which are the top two serotypes accounting for the majority of strains isolated from poultry slaughterhouses (Table 59, Figure 2) (source: Nippon AMR One Health Report 2021: Table 29), similarities between food-derived and poultry slaughterhouse-derived strains were found in respect of resistance to KM, SM, and TC in *S.* Infantis and resistance to KM and TC in *S.* Schwarzengrund. However, the fact that they showed a different trend from that seen in resistance rates among human-derived strains suggested the possibility that there are sources of these serotypes isolated from humans other than poultry and their food products.

Table 56. Resistance rates (%) of *Salmonella* spp. from poultry slaughterhouses

Agent	BP	Animal species	2012	2013	2014	2015	2016	2017	2018	2019	2020
ABPC	32*	Chickens	31.9	22.9	17.2	13.0	13.5	8.0	6.8	5.6	1.8
CEZ	32 (8* from 2016)	Chickens	7.4	5.9	3.1	1.6	7.7	2.5	3.4	3.7	1.8
CTX	4*	Chickens	7.4	5.1	2.3	1.6	1.9	1.8	2.6	1.9	0.9
MEPM	4*	Chickens	—	—	—	—	—	—	0.0	0.0	0.0
SM	32	Chickens	77.7	84.7	85.9	76.4	77.9	60.7	77.8	33.6	48.6
GM	16*	Chickens	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	64*	Chickens	31.9	42.4	57.8	69.1	72.1	73.2	66.7	75.7	68.8
TC	16*	Chickens	74.5	82.2	85.2	83.7	82.7	77.7	77.8	69.2	73.4
CP	32*	Chickens	0.0	0.8	1.6	1.6	0.0	0.9	1.7	0.9	0.0
CL	16 (4* from 2016)	Chickens	0.0	0.0	0.0	0.0	0.0	0.0	0.9	1.9	0.0
NA	32*	Chickens	29.8	19.5	17.2	15.4	12.5	17.0	18.8	8.4	11.9
CPFX	4 (1* from 2016)	Chickens	0.0	0.0	0.0	0.0	0.0	0.0	0.9	0.9	0.9
ST	76/4*	Chickens	31.9	48.3	51.6	57.7	56.7	55.4	53.0	52.3	45.9
Strains tested (n)		Chickens	94	118	128	123	104	112	117	107	109

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

Table 57. Serotypes of *Salmonella enterica* derived from poultry slaughterhouses (FY2015-2020)

Serotypes	Number of strains isolated	(%)
Schwarzengrund	449	66.8
Infantis	148	22.0
Typhimurium	35	5.2
Agon	12	1.8
Manhattan	11	1.6
Others	17	2.5
Total	672	100

Table 58. Serotypes of *Salmonella enterica* derived from poultry slaughterhouses, food, and humans (FY2015-2020)

From poultry slaughterhouses (n=672)	%	From food (n=715)*	%	From humans (n=1947)*	%
Schwarzengrund	66.8	Schwarzengrund	47.7	Enteritidis	12.6
Infantis	22.0	Infantis	24.6	4:i:-	11.1
Typhimurium	5.2	Manhattan	8.4	Infantis	9.6
Agona	1.8	Heidelberg	2.4	Thompson	7.9
Manhattan	1.6	Enteritidis	1.8	Saintpaul	6.4
Others	2.5	Others	15.1	Typhimurium	6.1
Total	100	Total	100	Schwarzengrund	5.1
				Newport	3.0
				Stanley	3.0
				Agona	2.0
				Others	33.3
				Total	100.0

*Source: Nippon AMR One Health Report 2021: Table 19

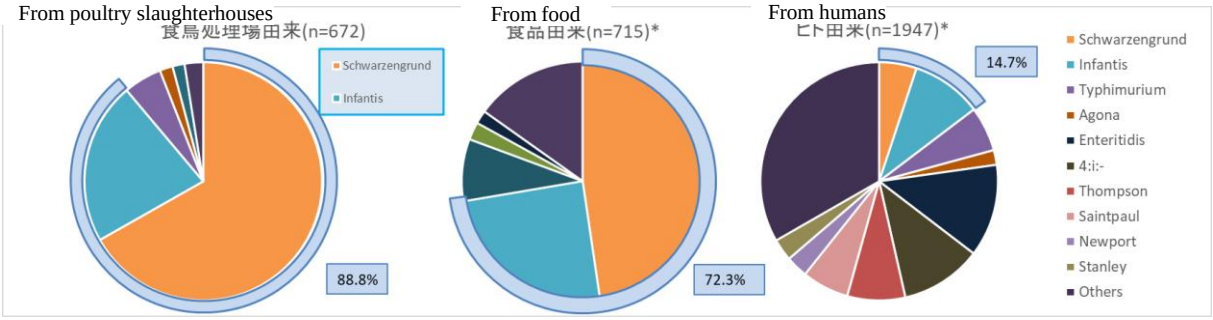

Figure 1. Proportions of the top 2 serotypes of *Salmonella enterica* derived from poultry slaughterhouses isolated in food and humans (2015-2020)
(figures for proportions in human-derived and food-derived strains are quoted from Nippon AMR One Health Report 2021: Table 19)

Table 59. Resistance rates (%) of *S.* Infantis and *S.* Schwarzengrund strains isolated from poultry slaughterhouses (chicken), food, and humans (2015-2020)

	Infantis			Schwarzengrund		
	Chicken (n=148)	Food (n=176)*	Humans (n=187)*	Chicken (n=449)	Food (n=341)*	Humans (n=98)*
ABPC	6.8	11.9	2.7	1.1	6.2	3.1
GM	0.0	0.6	0.0	0.0	0.0	0.0
KM	50.0	39.8	13.4	85.3	82.1	62.2
SM	65.5	74.4	30.5	63.3	80.4	71.4
TC	77.7	78.4	37.4	81.5	87.7	70.4
CP	1.4	2.3	2.1	0.7	8.8	1.0
CTX	4.7	6.8	1.6	0.9	0.6	2.0
NA	4.1	5.7	6.4	8.7	21.1	14.3
CPFX	0.0	0.0	0.0	0.7	0.3	0.0

*Source: Nippon AMR One Health Report 2020: Table 29

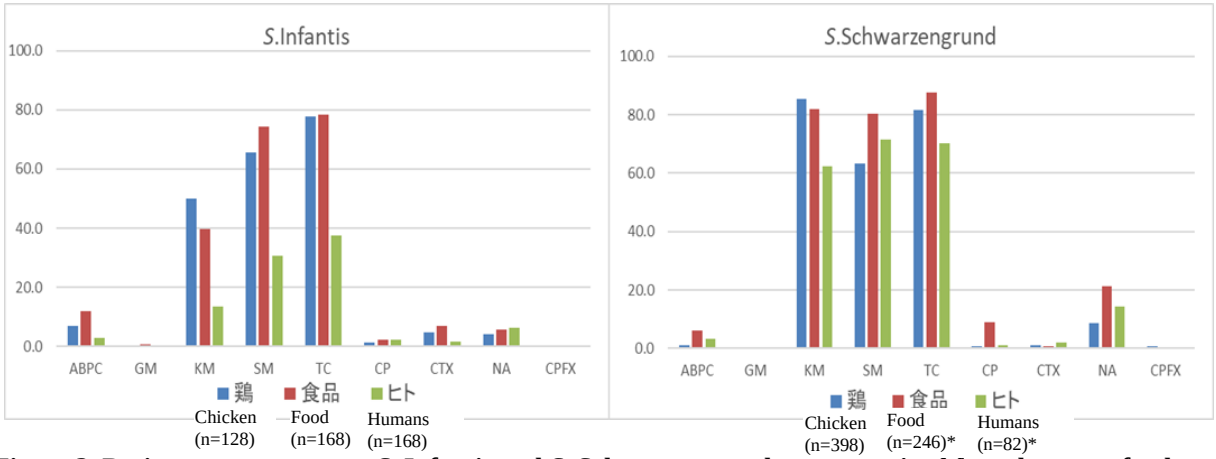

Figure 2. Resistance rates among *S.* Infantis and *S.* Schwarzengrund strains derived from humans, food, and poultry slaughterhouses (2015-2020)

(figures for resistance rates in human-derived and food-derived strains are quoted from Nippon AMR One Health Report 2021: Table 29)

2) Farm-raised aquatic animals

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

For the monitoring and surveillance of antimicrobial resistance in marine aquaculture sector under the JVARM, antimicrobial susceptibility monitoring is conducted focusing on *Lactococcus garvieae*, *Photobacterium damselae* subsp. *Piscicida* and *Vibrio* spp. that are derived from diseased fish and on *Vibrio parahaemolyticus* that is derived from aquaculture environment. Strains that were isolated and identified from diseased fish at prefectural fisheries experiment stations were mainly used for testing. Between 2011 and 2016, strains were provided by 4 to 6 prefectures per year, increasing to 8 in 2017, 12 in 2018, 11 in 2019, and 11 in 2020. In antimicrobial susceptibility tests, MIC values were measured using a broth microdilution method or an agar plate dilution method compliant with the CLSI Guidelines. For antimicrobial agents with a BP established by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents were determined microbiologically (midpoint of a bimodal MIC distribution).

To further enhanced surveillance of trends in antimicrobial resistance in marine aquaculture sector, the scope of surveillance was expanded to all farmed fishes in FY2017 and antimicrobial susceptibility monitoring of *Lactococcus garvieae* and *Vibrio* spp. is now being carried out.

i. *Lactococcus garvieae* derived from diseased fish

The monitoring of antimicrobial resistance from 2011 to 2020 was conducted on 4 agents that had been approved as a fisheries medicine. In 2020, resistance to LCM was 53.8%. Resistance rates remained low at 0.6% for both EM and OTC in 2020. As the MIC distribution of florfenicol (FF) was not bimodal, the BP could not be established, and the resistance rate could therefore not be calculated. However, MIC value was 8, with an increasing trend. (Table 60).

Table 60. Resistance rates (%) of *Lactococcus garvieae*

Agent*1	BP (～2019)	BP (2020～)	2011	2012	2013	2014	2015	2016	2017*2*3	2018	2019	2020
EM	8	8	0.0	10.3	0.0	0.0	3.7	8.0	1.9	0.0	3.1	0.6
LCM	4	4	92.6	76.9	71.4	62.5	59.3	76.0	61.0	31.5	55.2	53.8
OTC	8	16	0.0	12.8	0.0	0.0	3.7	8.0	0.0	0.0	2.6	0.6
Strains tested (n)			27	39	21	16	27	25	105	149	194	158

The unit of BP is μg/mL.

*1: While FF was also included in the scope of survey, the proportion of FF-resistant strains was not listed because BP could not be established.

*2: Monitoring focused only on *Seriola* until 2016, but was expanded in 2017 to include strains derived from all farmed fish species.

*3: An agar plate dilution method was used in monitoring until 2016, but the broth microdilution method has been used since 2017.

ii. *Photobacterium damselae* subsp. *piscicida* derived from diseased fish (Amberjacks)

The monitoring of antimicrobial resistance from 2011 to 2016 was conducted on 5 agents that had that had been approved as a fisheries medicine against pseudotuberculosis. The number of tested strains was small, with just 3 being tested in 2015, while no strains were isolated at all in 2016. In strains tested between 2011 and 2014, the resistance rate varied particularly for ABPC and for oxolinic acid (OA). However, the resistance rate remained at 7.1% or lower both for bicozamycin (BCM) and for fosfomycin (FOM). Although the proportion of FF resistant strains was not calculated given that no bimodal MIC distribution was observed, MIC values were low (≤ 1 μg/ml) in all strains, suggesting that the susceptibility was maintained. The strains tested in 2015 showed a low MIC value to all the tested agents (Table 61).

Table 61. Resistance rates (%) of pseudotuberculosis-causing bacteria (*Photobacterium damselae* subsp. *piscicida*)

Agent*	BP	2011	2012	2013	2014
ABPC	2	11.8	17.6	7.1	59.4
FOM	32	0.0	0.0	7.1	0.0
BCM	64	0.0	0.0	0.0	0.0
OA	1	100.0	82.4	92.9	3.1
Strains tested (n)		17	17	14	32

The unit of BP is μg/mL.

* While FF was also included in the scope of survey, its resistance proportion is not listed because BP cannot be established. No data for 2015 are shown, because only three strains were tested.

No strains were isolated at all in 2016.

iii. *Vibrio* spp.

Monitoring of 4 agents that had been approved as a fisheries medicine against vibriosis has been carried out since 2017 in respect of strains derived from diseased fish. In 2020, resistance to OTC was 11.9%. FF was not bimodal and almost all bacterial strains showed low MIC values (≤2 μg/ml). Although the MIC distribution of OA was not bimodal, all strains showed low MIC values (≤1 μg/ml), which suggested that susceptibility to these agents was maintained. Sulfamonomethoxine (SMMX), however, did not show clear bimodal MIC distribution, so the resistance rate could not be calculated (Table 62).

Table 62. Trends in resistance rates among *Vibrio* spp. (%)

Agent*	BP (-2017)	BP (2018-)	2017	2018	2019	2020
OTC	4	8	12.8	15.7	0.0	11.9
Strains tested (n)			39	51	40	42

The unit of BP is μg/mL.

* While FF, OA and SMMX were also included in the scope of survey, their resistance proportion were not listed because BP cannot be established.

iv. *Vibrio parahaemolyticus* derived from aquaculture environment

Monitoring of five agents approved as a fisheries medicine (EM, LCM, OTC, OA, and FF) was carried out using 53 and 50 strains derived from aquaculture environments in 2011 and 2012, respectively.

Given that no bimodal MIC distribution was observed for any of these agents, the proportion of the strain that was resistant to those agents was not calculated. MIC values, however, were low (EM:MIC≤2 μg/ml、OTC and FF:MIC≤1 μg/ml, OA:MIC≤0.5 μg/ml) in all strains, excluding lincomycin (32≤MIC ≤ 256 μg/ml for LCM), which suggested that the susceptibility was maintained to these agents.

3) Companion animals

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Routine monitoring of antimicrobial resistance in bacteria derived from diseased dogs and cats was launched in FY2017, as part of efforts to strengthen monitoring under the AMR Action Plan. Monitoring of antimicrobial resistance in bacteria derived from diseased animals, as opposed to those from healthy animals, has the potential to be affected by the use of antimicrobials in treatment or by the incidence of diseases. As with food-producing animals, obtaining information about antimicrobial resistance trends in healthy companion animals to serve as a baseline is considered important. Accordingly, as well as ongoing monitoring of diseased animals, surveillance of healthy dogs and cats was launched in 2018.

Antimicrobial susceptibility tests measured the MIC values of antimicrobials in respect of the bacterial strains collected, using a broth microdilution method compliant with the CLSI Criteria. For agents with a BP indicated by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents used EUCAST values or were determined microbiologically (midpoint of a bimodal MIC distribution).

a. Bacterial strains from diseased dogs and cats

Bacterial strains from diseased dogs and cats were collected from small-animal clinical laboratories. The country was divided into six regional blocks—Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku and Shikoku, and Kyushu and Okinawa—and the number of strains allocated on the basis of the number of notifications of veterinary clinic (small animal and other animals) establishment received.

Samples of *Escherichia coli* and *Klebsiella* spp. were collected from urine and reproductive organs, samples of coagulase-positive *Staphylococcus* spp. from urine and skin, and samples of *Enterococcus* spp. from urine and ears.

i. *Escherichia coli*

In 2021, rates of resistance to ABPC or NA were high, ranging from 54.4to 59.4%. On the other hand, the rate of resistance to GM, KM, CP or ST in strains isolated from dogs and cats was less than 20%. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains respectively were as follows: 27.8% and 29.4% to CTX, 40.6% and 41.2% to CPFX, 0.0% and 0.6% to CL, and both 0.0% to MEPM, respectively.

Table 63. Resistance rates (%) of *Escherichia coli* derived from diseased dogs and cats

Agent	BP	Animal species	2017	2018	2019	2020	2021
ABPC	32*	Dog	55.3	63.0	51.1	50.3	54.4
		Cat	64.0	65.6	60.2	56.5	59.4
CEZ	32*	Dog	31.2	47.4	30.3	31.1	32.8
		Cat	37.5	49.5	32.0	29.8	33.5
CEX	32†	Dog	31.7	42.9	31.5	32.8	32.8
		Cat	41.9	47.3	31.3	31.7	37.1
CTX	4*	Dog	26.1	41.6	26.4	27.1	27.8
		Cat	33.8	39.8	26.6	26.1	29.4
MEPM	4*	Dog	0.0	0.0	0.0	0.0	0.0
		Cat	0.0	0.0	0.0	0.0	0.0
SM	32†	Dog	29.6	29.9	20.2	27.1	25.6
		Cat	32.4	34.4	28.9	19.3	23.5
GM	16*	Dog	14.1	18.8	12.9	13.0	12.2
		Cat	12.5	15.1	9.4	9.9	17.1
KM	64*	Dog	6.5	7.8	5.1	5.6	5.6
		Cat	8.1	12.9	7.0	3.7	6.5
TC	16*	Dog	28.1	27.3	21.3	23.2	20.6
		Cat	24.3	28.0	26.6	16.8	24.1
CP	32*	Dog	12.6	16.9	11.8	7.9	12.8
		Cat	13.2	15.1	7.8	5.0	8.2
CL	4*	Dog	1.0	0.0	0.0	0.0	0.0
		Cat	0.0	1.1	0.0	0.6	0.6
NA	32*	Dog	61.8	72.7	56.2	58.8	56.1
		Cat	58.8	68.8	46.9	55.9	54.7
CPFX	4* (1*since 2018)	Dog	43.2	55.2	38.8	42.4	40.6
		Cat	39.0	50.5	37.5	38.5	41.2
ST	76/4*	Dog	24.6	27.9	17.4	19.2	18.3
		Cat	22.1	34.4	22.7	14.3	21.8
Strains tested (n)		Dog	199	154	178	177	180
		Cat	136	93	128	161	170

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

† BP follows EUCAST Criteria.

ii. *Klebsiella* spp.

Of the *Klebsiella* spp., *K. pneumoniae* was the most commonly collected, with *K. oxytoca* and *K. aerogenes* being the others collected. In 2021, resistance to CEZ, cephalexin (CEX), NA, or CPFX was observed to exceed 40% in dog- and cat-derived strains, as was resistance to CTX, SM, GM, TC, or ST in cat-derived strains. On the other hand, resistance to KM was below 10% in strains derived from both dogs and cats. Looking at rates of resistance in dog- and cat-derived strains to critically important antimicrobials for human medicine, resistance to CTX was 37.4% and 56.0%, respectively, resistance to CPFX was 49.5% and 73.3%, respectively, and resistance to CL was 0.0%, 4.0%, respectively. Resistance to MEPM was both 0.0%.

Table 64. Resistance rates (%) of *Klebsiella* spp. derived from diseased dogs and cats

Agent	BP	Animal species	2017	2018	2019	2020	2021
CEZ	32*	Dog	47.2	51.0	42.0	45.8	44.0
		Cat	84.6	90.0	67.6	61.3	69.3
CEX	32†	DOg	44.4	46.9	42.0	45.8	44.0
		Cat	84.6	80.0	62.2	58.1	64.0
CTX	4*	Dog	41.7	36.7	34.6	34.9	37.4
		Cat	80.8	75.0	56.8	48.4	56.0
MEPM	4*	Dog	0.0	0.0	0.0	0.0	0.0
		Cat	0.0	0.0	0.0	0.0	0.0
SM	32†	Dog	26.4	34.7	29.6	31.3	30.8
		Cat	57.7	55.0	59.5	41.9	52.0
GM	16*	Dog	26.4	28.6	21.0	28.9	24.2
		Cat	61.5	55.0	40.5	33.9	44.0
KM	64*	Dog	8.3	12.2	6.2	10.8	9.9
		Cat	23.1	20.0	13.5	12.9	9.3
TC	16*	Dog	33.3	42.9	30.9	33.7	26.4
		Cat	57.7	65.0	48.6	40.3	56.0
CP	32*	Dog	25.0	32.7	19.8	25.3	20.9
		Cat	26.9	45.0	16.2	25.8	26.7
CL	4*	Dog	1.4	0.0	0.0	0.0	0.0
		Cat	3.8	0.0	0.0	1.6	4.0
NA	32*	Dog	51.4	61.2	46.9	48.2	54.9
		Cat	84.6	95.0	81.1	54.8	77.3
CPFX	4* (1*since 2018)	Dog	44.4	57.1	46.9	44.6	49.5
		Cat	84.6	90.0	75.7	56.5	73.3
ST	76/4*	Dog	41.7	46.9	37.0	39.8	38.5
		Cat	76.9	70.0	56.8	43.5	54.7
Strains tested (n)		Dog	72	49	81	83	91
		Cat	26	20	37	62	75

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

†EUCAST values were used as the BP for CEX. As EUCAST has not set a BP for SM, the JVARM value (midpoint of a bimodal MIC distribution obtained in FY2001) was used. Surveillance also covered ABPC, but the figures are not given here, due to the intrinsic resistance of *K. pneumoniae* and *K. oxytoca*.

iii. Coagulase-positive *Staphylococcus* spp.

The most common coagulase-positive *Staphylococcus* spp. in both dogs and cats was *S. pseudintermedius*. *S. aureus*, *S. schleiferi* subsp. *coagulans*, and *S. intermedius* were also collected.

In *S. pseudintermedius*, resistance to all agents except GM in dog- t-derived strains was observed to exceed 50% in 2021. More than 70% of strains isolated from both dogs and cats were observed to be resistant to AZM and CPFX, which are critically important antimicrobials for human medicine.

In *S. aureus* isolated from cats, resistance to benzylpenicillin (PCG), MPIPC) CEZ, CEX, CFX, CTX, GM, EM, AZM, or CPFX was observed to exceed 50% in 2021. On the other hand, the resistance rate to SM was low (3.7%). Rates of resistance to CTX, AZM, or CPFX, which are critically important antimicrobials for human medicine, were observed to be more than 50%.

Table 65. Resistance rates (%) of *Staphylococcus pseudintermedius* derived from diseased dogs and cats

Agent*	BP	Animal species	2017	2018	2019	2020	2021
PCG	0.25†	dog	-	-	97.4	95.9	97.4
		cat	-	-	97.6	98.0	98.4
MPIPC	0.5†	dog	58.2	56.6	62.8	51.4	56.6
		cat	68.6	81.8	81.0	77.6	78.7
GM	16†	dog	26.2	54.2	64.1	25.7	40.8
		cat	13.7	63.6	52.4	44.9	50.8
TC	16†	dog	62.3	67.5	66.7	73.0	71.1
		cat	52.9	81.8	85.7	71.4	85.2
CP	32†	dog	43.4	49.4	60.3	58.1	55.3
		cat	64.7	72.7	83.3	67.3	82.0
EM	8†	dog	67.2	74.7	79.5	77.0	71.1
		cat	70.6	86.4	95.2	79.6	91.8
AZM	8†	dog	67.2	74.7	79.5	77.0	71.1
		cat	66.7	86.4	95.2	79.6	91.8
CPFX	4†	dog	64.8	75.9	75.6	74.3	73.7
		cat	88.2	100.0	97.6	93.9	91.8
Strains tested (n)		dog	122	83	78	74	76
		cat	51	22	42	49	61

The unit of BP is μg/mL.

† BP follows CLSI Criteria.

While ABPC, CEZ, CEX, CFX, CMZ, CTX and SM were also included in the scope of monitoring, the proportion of ABPC-, CEZ-, CEX-, CFX-, CMZ-, CTX- and SM-resistant strains were not listed because BP could not be established.

Table 66. Resistance rates (%) of *Staphylococcus aureus* derived from diseased cats

Agent	BP	Animal species	2017	2018	2019	2020	2021
PCG	0.25	cat	-	-	90.0	84.6	96.3
MPIPC	4†	cat	61.9	70.6	70.0	65.4	51.9
CEZ	4$	cat	61.9	64.7	66.7	57.7	44.4
CEX	16$	cat	61.9	70.6	70.0	61.5	59.3
CFX	8$	cat	61.9	64.7	70.0	61.5	51.9
CTX	8$	cat	61.9	64.7	70.0	61.5	55.6
SM	32$	cat	4.8	5.9	0.0	3.8	3.7
GM	16†	cat	47.6	58.8	36.7	57.7	22.2
TC	16†	cat	14.3	41.2	43.3	38.5	14.8
CP	32†	cat	0.0	0.0	0.0	0.0	3.7
EM	8†	cat	66.7	76.5	70.0	61.5	70.4
AZM	8†	cat	66.7	76.5	70.0	61.5	70.4
CPFX	4†	cat	61.9	76.5	83.3	73.1	63.0
Strains tested (n)		cat	21	17	30	26	27

The unit of BP is μg/mL.

† BP follows CLSI Criteria. $ Uses EUCAST's ECOFF value

* While ABPC and CMZ were also included in the scope of monitoring, the proportion of ABPC- and CMZ-resistant strains were not listed because BP could not be established.

iv. *Enterococcus* spp.

The most common *Enterococcus* spp. in both dogs and cats was *E. faecalis*, followed by *E. faecium*. In 2021, rates of resistance to TC were the highest in both dog- and cat-derived strains (63.9% in dogs and 65.9% in cats), followed by EM (46.1% in dogs and 45.9% in cats), and the resistance rate to ABPC in dog-derived strains and to CP in dog- and cat-derived strains were less than 20%. For CPFX, an important antimicrobial agent in human medicine, 27.8% and 40.6% of dog- and cat-derived strains were found to be resistant, respectively. Measurement of VCM as a test agent began in 2019, and the resistance rates of both dog- and cat-derived strains were 0.0%.

Table 67. Resistance rates (%) of *Enterococcus* spp. derived from diseased dogs and cats

Agent*	BP	Animal species	2017	2018	2019	2020	2021
ABPC	16 †	dog	26.7	20.5	20.0	14.6	13.3
		cat	17.3	31.6	33.0	26.4	24.1
GM	32 §	dog	22.9	15.4	25.2	25.7	27.8
		cat	19.4	24.6	25.2	25.7	27.1
TC	16 †	dog	65.6	67.9	68.9	64.9	63.9
		cat	70.4	73.7	64.1	68.2	65.9
CP	32 †	dog	20.6	14.1	18.5	14.6	13.3
		cat	20.4	15.8	8.7	18.2	15.3
EM	8 †	dog	61.8	39.7	43.0	45.0	46.1
		cat	41.8	54.4	39.8	48.0	45.9
CPFX	4 †	dog	42.7	28.2	31.1	25.1	27.8
		cat	34.7	49.1	43.7	40.5	40.6
VCM	32 †	dog	-	-	0.0	0.0	0.0
		cat	-	-	0.0	0.0	0.0
Strain tested (n)		dog	131	78	135	171	180
		cat	98	57	103	148	170

The unit of BP is μg/mL.

* While AZM was also included in the scope of monitoring, the proportion of AZM-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

§ As EUCAST has not set a BP for GM, the JVARM value (midpoint of a bimodal MIC distribution obtained in FY2002) was used.

b. Bacterial strains from healthy dogs and cats

Bacterial strains from healthy dogs and cats were collected from veterinary clinics across the country with the cooperation of the Japan Veterinary Medical Association, with the number of strains allocated on the basis of the number of notifications of veterinary clinic (small animal and other animals) establishment received by each prefecture. Rectal swabs were taken from healthy dogs and cats brought to veterinary clinics for health checkups and vaccination. *Escherichia coli* and *Enterococcus* spp. were then isolated from the samples, identified, and sent for antimicrobial susceptibility tests.

i. *Escherichia coli*

In strains isolated from healthy dogs and cats, the rates of resistance to ABPC or NA showed a high trend in 2021. Resistance rates to all agents other than ABPC in cat-derived strains were less than 20%. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains were as follows: 7.8% and 7.5% to CTX, and 7.1% and 7.5% to CPFX, while the resistance rates to MEPM or CL were both 0.0%. In all agents which resistant strains had been found, resistance rates of *Escherichia coli* derived from healthy dogs and cats were lower than that from diseased dogs and cats collected in same year.

Table 68. Resistance rates (%) of *Escherichia coli* derived from healthy dogs and cats

Agent	BP	Animal species	2018	2019	2020	2021
ABPC	32*	dog	33.8	23.3	29.5	17.5
		cat	28.5	27.1	18.5	21.7
CEZ	32*	dog	19.2	11.4	17.8	10.4
		cat	17.1	13.3	7.5	9.9
CEX	32†	dog	17.9	11.4	17.1	9.7
		cat	18.4	13.3	8.9	10.6
CTX	4*	dog	13.2	8.8	13.0	7.8
		cat	10.8	6.4	2.7	7.5
MEPM	4*	dog	0.0	0.0	0.0	0.0
		cat	0.0	0.0	0.0	0.0
SM	32†	dog	19.2	13.0	14.4	8.4
		cat	11.4	11.7	8.9	11.2
GM	16*	dog	3.3	2.6	8.2	1.9
		cat	2.5	4.3	3.4	4.3
KM	64*	dog	5.3	3.6	4.1	2.6
		cat	1.9	3.2	3.4	3.1
TC	16*	dog	16.6	13.0	12.3	8.4
		cat	10.8	10.1	8.2	8.1
CP	32*	dog	4.6	5.7	5.5	3.2
		cat	1.3	3.7	1.4	2.5
CL	4*	dog	0.0	0.0	0.0	0.0
		cat	0.0	0.0	0.0	0.0
NA	32*	dog	27.8	20.7	22.6	10.4
		cat	24.7	28.7	17.8	17.4
CPFX	1*	dog	18.5	8.8	12.3	7.1
		cat	12.0	13.3	4.8	7.5
ST	76/4*	dog	13.2	7.8	11.6	5.8
		cat	12.0	9.6	5.5	7.5
Strains tested (n)		dog	151	193	146	154
		cat	158	188	146	161

The unit of BP is μg/mL.

*BP follows CLSI Criteria.

†BP follows EUCAST Criteria.

ii. *Enterococcus* spp.

The most common *Enterococcus* spp. in both dogs and cats were *E. faecalis*. *E. faecium*, *E. gallinarum*, *E. durans*, *E. hirae*, *E. avium*, *E. casseliflavus*, and *E. raffinosus* were also collected. In strains isolated from dogs and cats in 2021, the highest rate of resistance was to TC, followed by EM, while rates of resistance to the other antimicrobials were all less than 20%. The rates of resistance to critically important antimicrobial for human medicine CPFX in dog- and cat-derived strains were 5.5 and 4.8%, and both 0.0% to VCM.

Table 69. Resistance rates (%) of *Enterococcus* spp. derived from healthy dogs and cats

Agent*	BP	Animal species	2018	2019	2020	2021
ABPC	16 †	dog	6.9	1.9	5.4	0.0
		cat	2.2	3.4	1.3	1.2
GM	32 §	dog	12.4	7.0	14.0	10.2
		cat	11.1	15.7	22.1	11.9
TC	16 †	dog	55.9	41.8	43.4	47.7
		cat	48.9	61.8	44.2	58.3
CP	32 †	dog	15.9	10.1	10.1	11.7
		cat	11.1	14.6	14.3	15.5
EM	8 †	dog	32.4	23.4	27.9	23.4
		cat	34.4	34.8	32.5	38.1
CPFX	4 †	dog	13.8	5.7	10.1	5.5
		cat	14.4	13.5	10.4	4.8
VCM	32 †	dog	0.0	0.0	0.0	0.0
		cat	0.0	0.0	0.0	0.0
Strains tested (n)		dog	145	158	129	128
		cat	90	89	77	84

The unit of BP is μg/mL.

* While AZM was also included in the scope of monitoring, the proportion of AZM-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

§ As EUCAST has not set a BP for GM, the JVARM value (midpoint of a bimodal MIC distribution obtained in FY2002) was used.

4) Wild animals

Antimicrobial susceptibility tests were conducted on 963 strains of *Escherichia coli* isolated from 475 wild animals (525 strains from 242 deer; 224 strains from 112 wild boar; 199 strains from 113 small mammals (including brown rats, black rats, large Japanese field mice, and Japanese shrew moles); 10 strains from 4 badgers; 3 strains from 2 feral cattle ((Japanese native cattle *Tokara-Ushi*); and 2 strains from 2 Amami rabbits) within Japan between 2013 and 2017 (Table 70). Strains isolated from deer and wild boar demonstrated resistance to 8 agents, while those isolated from small mammals showed resistance to 10 agents. Resistant bacteria were observed in 5.9% of strains isolated from deer, with resistance to tetracycline (TC, 4.4%) highest, followed by colistin (1.5%), ABPC, and sulfamethoxazole-trimethoprim (ST, 0.8%). Resistance was observed in 8.0% of strains isolated from wild boar, with resistance to TC (4.0%) highest, followed by ABPC (3.6%), and CP (1.8%). Resistant strains accounted for 18.1% of strains isolated from small mammals, with resistance to ABPC and TC (12.6% in both cases) highest, followed by ST (11.6%). In particular, in the case of small mammals, most of antimicrobial- resistant strains were observed in strains from facilities related to food-producing livestock, with resistance to ABPC, ST, TC, and NA observed to be in excess of 10%. However, resistance to only 2 agents (TC and ST) was found in strains isolated from urban areas and no resistance to any of the 12 agents monitored was found in strains isolated from mountainous areas. Bacteria producing extended-spectrum beta-lactamase (ESBL) were observed in 1 strain isolated from small mammals (livestock facility) and the ESBL was found to be CTX-M-1.

While the effects of antimicrobial-resistant bacteria contamination of habitats can be seen in the distribution of resistant bacteria in land-dwelling wild animals, the rates are low compared with food-producing animals and companion animals. 848 *E. coli* isolates from wild deer from 2016 to 2019 also showed a low rate of agent-resistance (9 isolates, 1.1%), although the antimicrobials tested varied (Table 71). Thus, antimicrobial-resistant bacterial contamination of the mountainous areas that form the main habitat of the deer and wild boar covered by this study appeared to be low.

In addition, 135 strains of *E. coli* from the Amami rabbit inhabiting a remote island (Amami Oshima) from 2017 to 2020 were susceptible to the antimicrobials tested. Future research is expected to determine whether Amami rabbit, which mainly feeds on grasses and trees, has less opportunity to receive resistant bacteria from humans, domestic animals, and even other wildlife.

Among 144 *E. coli* strains isolated from common cormorants caught in Gunma, Gifu, Shiga, and Oita prefectures from 2018 to 2019, 5.6% were resistant, and resistance were observed to ABPC (3.5%), TC (2.8%), NA (1.4%), CPFX (0.7%), CL (0.7%), CP (1.4%), and ST (1.4%). In 110 *E. coli* isolates from white-fronted goose feces collected in Miyajima-numa (Hokkaido, Japan) in 2019, one (0.9%) was resistant (ABPC-CEZ resistant) and carried a plasmidic resistance gene (bla_{ACC}). Although it must be taken into account that the fact that the common cormorant is a resident bird and the white-fronted goose is a migratory bird affects the distribution of resistant strains, attention must be paid to the spread of resistant bacteria and contamination of the aquatic environment through wild waterfowl, as fluoroquinolone-resistant and transmissible β-lactamase-producing strains were isolated from wild waterfowl.

750 *E. coli* strains isolated from the faeces of 274 (75%) of 366 wild animals in Japan between 2018 and 2021 (517 isolates from 189 of 243 deer, 33 isolates from 12 of 43 nutria, 61 isolates from 22 of 22 civets, 54 isolates from 18 of 18 wild boars, 24 isolates from 8 of 8 raccoon dogs, 9 isolates from 5 of 5 badgers, 11 isolates from 4 of 4 weasels, 11 isolates from 4 of 4 foxes, 7 isolates from 4 of 4 small Japanese field mouse, 9 isolates from 3 of 3 Japanese macaques, 2 isolates from of 1 of 2 raccoons, 6 isolates from 2 of 2 wild cats, 3 isolates from 1 of 1 bear, 3 isolates from 1 of 1 marten) were tested for drug susceptibility.

Antimicrobial resistance was found in *E. coli* from deer (5.4%, 28/517), civet (1.6%, 1/61), wild boar (7.4%, 4/54), badger (11%, 1/9), fox (9.1%, 1/11), Japanese monkey (11.1%, 1/9) and raccoon (50%, 1/2). Resistance was observed to five agents in the fox-derived strain, four drugs in the deer-derived strain and one drug in the civet, wild boar, Japanese macaque and common raccoon-derived strains (Table 72). Overall, tetracycline (TC, 5.4%) resistance was the highest, and resistance to six other drugs was observed. The CIP-resistant strains found in foxes were multidrug-resistant strains to ABPC, TC and CP.

CTX-resistant and quinolone-resistant *E. coli* were isolated on DHL agar medium containing antimicrobials. CTX-resistant *E. coli* isolated on cephalosporin (CEZ, cephalexin or CTX)-containing media were isolated from 5 of 366 (1.4%, 14 strains). Isolates were from 2 of 243 deer (0.8%, 6 strains), 1 of 6 badgers (16.7%, 2 strains), 1 of 4 foxes (25%, 3 strains), and 1 of 2 raccoons (50%, 2 strains). One strain from foxes was a CMY-2 β-lactamase-producing strain, while the others were CTX-M type β-lactamase (CTX-M-27, CTX-M-55 and CTX-M-1) producers. 35 strains of quinolone-resistant E. coli were isolated from 17 of 366 (4.6%) specimens on NA-containing media, and the animals were deer (10, 4.1%), civet (1, 13.6%), raccoon dogs (1, 12.5%), fox (2, 50%) and common raccoon (1, 50%).

Quinolone-resistant strains showed mutations in the quinolone resistance-determining region (QRDR) of DNA gyrase or topoisomerase IV, and some strains carried a plasmid-mediated quinolone resistance gene (*qnr*B19). Investigations in combination with antimicrobial-containing media are expected to clarify the actual status of antimicrobial-resistant bacteria in wild animals.

Table 70. Resistance rates (%) of *Escherichia coli* derived from wild animals from 2013 to 2017

Agent (BP)	Deer				Wild boar	Small mammals				Other		
	Mountains	Shrines	Parks	Subtotal	Mountains	Livestock facilities	Urban areas	Mountains	Subtotal	Badgers	Kuchinoshima cattle	Amami rabbits
Number of strains	327	102	96	525	224	106	47	46	199	10	3	2
Number of resistant*	15	5	11	31	18	30	6	0	36	4	2	1
Resistance rate (%)	4.6	4.9	11.5	5.9	8.0	28.3	14.0	0	18.1	40.0	66.7	50.0
ABPC(32)	0.6	2.0	0	0.8	3.6	23.6	0	0	12.6	10	0	0
CEZ(32)	0	0	0	0	0	2.8	0	0	1.5	0	0	0
CTX(4)	0	0	0	0	0	1.9	0	0	1.0	0	0	0
MEPM(2)	0	0	0	0	0	0	0	0	0	0	0	0
GM(16)	0.3	0	0	0.2	0.4	2.8	0	0	1.5	0	0	0
KM(64)	0.9	0	0	0.6	1.3	5.7	0	0	3.0	20	0	0
TC(16)	3.1	2.0	11.5	4.4	4.0	17.9	12.8	0	12.6	20	33.3	0
NA(32)	0.9	0	0	0.6	0.9	11.3	0	0	6.0	0	0	0
CPFX(2)	0.3	0	0	0.2	0	0	0	0	0	0	0	0
CL(4)	1.2	2.9	1.0	1.5	1.3	3.8	0	0	2.0	10	33.3	50
CP(32)	0	0	0	0	1.8	1.9	0	0	1.0	0	0	0
ST(76/4)	0.6	2.0	0	0.8	0.9	18.9	6.4	0	11.6	0	0	0

The unit of BP is μg/mL.

* Number of strains that showed resistance to at least 1 antimicrobial agent.

Source: Asai T, Usui M, Sugiyama M, Izumi K, Ikeda T, Andoh M. Antimicrobial susceptibility of *Escherichia coli* isolates obtained from wild mammals between 2013 and 2017 in Japan. J Vet Med Sci. 82(3):345-349, 2020.

Table 71. Resistance rates (%) of *Escherichia coli* from wild animals

Agent (BP)	Deer (2016-2019)	Amami rabbit (2017~2020)	Great cormorant (2018~2019)	White-fronted goose (2019)
		Amami Oshima	Gunma, Gifu, Shiga, Oita	Miyajima swamp, Hokkaido
Number of strains	848	135	144	110
Number of resistant	9	0	8	1
Resistance rate (%)	1.1	0	5.6	0.9
ABPC (32)	0.1	0	3.5	0.9
CEZ (32)	0.1	0	0	0.9
CTX (4)	0	0	0	0
MEPM (2)	Not implemented	0	0	0
GM (16)	0	0	0	0
KM (64)	0	0	0	0
TC (16)	0	0	2.8	0
NA (16)	0	0	1.4	0
CPFX (2)	0	0	0.7	0
CL (4)	Not implemented	0	0.7	0
CP (32)	0.1	0	1.4	0
ST (76/4)	0.6	0	1.4	0

The unit of BP is μg/mL.

* Number of strains that showed resistance to at least 1 antimicrobial agent.

Source:

Deer: Tamamura-Andoh Y, Tanaka N, Sato K, Mizuno Y, Arai N, Watanabe-Yanai A, Akiba M, Kusumoto M. A survey of antimicrobial resistance in Escherichia coli J Vet Med Sci. 83(5):754-758, 2021.

Amami rabbit: Matsunaga N, Suzuki M, Andoh M, Ijiri M, Ishikawa K, Obi T, Chuma T, Fujimoto Y. Analysis of fecal samples from Amami rabbits (Pentalagus furnessi) indicates low levels of antimicrobial resistance in Escherichia coli. Eur J Wildl Res 66:, 84, 2020.

Great cormorant: Odoi JO, Sugiyama M, Kitamura Y, Sudo A, Omatsu T, Asai T. Prevalence of antimicrobial resistance in bacteria isolated from Great Cormorants（Phalacrocorax carbo hanedae）in Japan. J Vet Med Sci. 83(8):1191-1195, 2021.

White-fronted goose: Fukuda A, Usui M, Ushiyama K, Shrestha D, Hashimoto N, Sakata MK, Minamoto T, Yoshida O, Murakami K, Tamura Y, Asai T. Prevalence of antimicrobial-resistant Escherichia coli in migratory Greater White-fronted Goose (Anser albifrons) and their habitat in Miyajimanuma, Japan. Wildl Dis. 57(4): 954-958, 2021.

Table72. Resistance rate (%) of *Escherichia coli* isolated form wild animals from 2018 to 2021

Agent(BP)	Deer	Civeet	Wild boar	Nutria	Racoon dog	Fox	Weasel	Badger	Monkey	Small Japanese field mouse	Wild cat	Bear	Marten	Racoon
Number of strains	517	61	54	33	24	11	11	9	9	7	6	3	3	2
Number of resistance*	28	1	4	0	0	1	0	1	1	0	0	0	0	1
Resistance rate(%)	5.4%	1.6%	7.4%	0.0%	0.0%	9.1%	0.0%	11.1%	11.1%	0.0%	0.0%	0.0%	0.0%	50.0%
ABPC(32)	0.4	1.6	0	0	0	9.1	0	0	0	0	0	0	0	0
CEZ(32)	0.2	0	0	0	0	0	0	0	0	0	0	0	0	0
CTX(4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MEPM(2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GM(16)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
KM(64)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TC(16)	4.1	0	7.4	0	0	9.1	0	0	0	0	0	0	0	0
NA(16)	0	0	0	0	0	9.1	0	0	0	0	0	0	0	0
CPFX(2)	0	0	0	0	0	9.1	0	0	0	0	0	0	0	0
CL(4)	1.0	0	0	0	0	0	0	0	11.1	0	0	0	0	50
CP(32)	0	0	0	0	0	9.1	0	0	0	0	0	0	0	0
ST(76/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0

The unit of BP is μg/mL.

* Number of strains that showed resistance to at least 1 antimicrobial agent.

Source

Asai T, Usui M, Sugiyama M, Andoh M. A survey of antimicrobial-resistant Escherichia coli prevalence in wild mammals in Japan using antimicrobial-containing media. J Vet Med Sci. 84(12):1645-1652, 2022.

(3) Food

The status of foodborne resistant bacteria is based on the results of a research project (FY2021 Health and Labour Sciences Research Grant General Report on the Research Project to Promote Food Safety: "Research to strengthen the surveillance system for food-borne drug-resistant bacteria based on One Health" Principal Investigator Motoyuki Sugai). After each local public health institute (CHIKEN, 23 CHIKEN participating voluntarily) purchased commercial meat from the relevant region, *Salmonella*, *Campylobacter*, *E. coli*, and other bacteria contaminating the meat were cultured and isolated using selective media according to the protocols established thus far. Agent susceptibility of the isolated strains were tested for 12 agents by the CLSI disk diffusion method. The results for *Salmonella* are summarized in section (iv) ii, Non-typhoidal *Salmonella*, (local public health institutes) (see p. 29). In summary, for serotypes *S*. Infantis, *S*. Schwarzengrund, and *S*. Manhattan, food-derived isolates showed a high similarity to the agent-resistance rates and resistance patterns of human patient feces-derived isolates, suggesting a strong association between food-derived and human-derived resistant bacteria.

The emergence of agent-resistant strains of *Campylobacter*: *C. jejuni* and *C. coli* showed high rates of resistance to fluoroquinolone agents (56.1% and 68.8%, respectively). The resistance rate to EM, the first-line treatment for *Campylobacter* enteritis, was low in *C. jejuni* (1.5%).

Emergence of agent-resistant *E. coli* from commercial chicken meat: *E. coli* isolated from domestic chicken meat showed high resistance rates to TC (49.0%), SM (47.0%), and ABPC (42.4%). On the other hand, high resistance rates of *E. coli* isolated from foreign chicken meat were observed against TC (36.8%), ABPC (33.3%), and GM (21.1%), indicating that the trends of agent resistance were different between domestic- and foreign-derived strains. The cephalosporin resistance rates were 1.0% for domestic-derived strains and 3.5% for foreign-derived strains.

Regarding ESBL-producing genes, in *Salmonella*, the CTX-M-1 group was the most frequently possessed, followed by the TEM type, in both human- and food-derived strains. On the other hand, in *E. coli*, the CTX-M-9 group, CTX-M-2 group, and TEM type were frequently detected.

A multiplex PCR method was developed to detect colistin resistance genes *mcr*-1 to 10. The *mcr*-1 group (2 strains) was detected in *Salmonella* from human sources, and *mcr*-5 (1 strain) was detected in *Salmonella* from food sources. On the other hand, *mcr*-1 group (2 strains: EHEC and diarrheagenic strain) was detected in human-derived *E. coli*, but not in foodborne *E. coli*. Investigation of colistin resistance in animal-derived strains: *mcr*-1 and *mcr*-5 genes were identified in *E. coli*. No *mcr* genes were detected in *Salmonella* from poultry slaughterhouses. The use of colistin as a feed additive for livestock has been withdrawn in our country since 2018. It is necessary to track the transition of the already existing colistin resistance genes in the future.

Agent-resistant E. coli from feces of healthy subjects: the highest resistance rate was observed against ABPC (27.8%), followed by TC (21.7%) and NA (21.0%). Fluoroquinolone and cephalosporin resistances were 6.4% and 4.6%, respectively, similar to previous years. Colistin-resistant *mcr*-bearing strains accounted for 0.48%. The resistance rate of enteric *E. coli* in healthy individuals was considerably high.

(4) Environment

In general, waste resulting from human activities is discharged into the environment (rivers or oceans) after being treated at sewage treatment plants or other household wastewater treatment facilities until it meets effluent standards. Attention to environmental AMR based on the One Health approach focuses on evaluating the risks posed by antimicrobial-resistant bacteria (genes) by determining which antimicrobial-resistant bacteria (genes) exist in environmental water discharged into the environment (rivers and oceans) after waste resulting from human activities (rivers or oceans) is treated at sewage treatment plants or other household wastewater treatment facilities until it meets effluent standards, and considering how those antimicrobial-resistant bacteria (genes) could circulate into our daily lives and pose a risk to human health.

With few quantitative reports available at present concerning the extent to which antimicrobial-resistant bacteria (AMR bacteria: ARB) and the antimicrobial-resistance genes (AMR genes: ARGs) that stem from them are continuing to impose a burden after being excreted into the environment, a systematic nationwide survey is regarded as essential. Accordingly, a research group funded by a Ministry of Health, Labour and Welfare research grant has been formed for the purpose of conducting ongoing environmental AMR surveillance for the Japanese government. Led by Hajime Kanamori, the research group is conducting a study entitled "Research to Establish Methods of Surveying Antimicrobial-resistant Bacteria and Antimicrobials in the Environment" from 2018 to 2020. In FY 2008 - FY 2020, this research group prepared a procedure manual contributing to environmental AMR monitoring and conducted research to establish a method for investigating agent-resistant bacteria and residual antimicrobial agents in environmental water. A system was established to develop a nationwide environmental AMR monitoring survey of discharged treated water, and the actual environmental burden of local governments was elucidated at the genetic level. In addition, a domestic and international literature review was conducted to clarify the current status and issues related to agent resistance in the environment.

As an outcome of the four-year period (FY 2018-2021), next-generation sequencers were used to establish a comprehensive technique for sequencing ARGs (metagenomic analysis) in environmental water (Pathogen Genomics Center, National Institute of Infectious Diseases). Metagenomic analysis was then carried out on samples of wastewater from sewage treatment plants and effluent water provided by 39 local governments (446 samples in total, collected in summer (August) and winter (February) from August 2018 to February 2022). As a result of the 4-year (8 times) continuous survey, an increase or decrease in ARGs, presumably due to the impact of the new coronavirus outbreak, was confirmed from the winter of 2020 onwards. Fluctuation in ARGs, presumably due to the impact of the new coronavirus outbreak, was observed from winter 2020 onwards. Although sulphate (sulfonamide) resistance genes had been showing an increasing trend until winter 2020, they showed a marked decrease in summer 2020 and remained low for two years until winter 2022. Macrolide resistance genes once showed a decreasing trend in winter 2020, but in winter 2022 they were found to have increased to the levels prior to the new coronavirus outbreak.

A similar downward trend was also seen in quinolone resistance genes, suggesting a relationship to a decline in the use of quinolones in humans. However, a deviation was seen from the situation in regard to the isolation of quinolone-resistant *Escherichia coli*. As the research group's metagenomic analysis technique focuses on detecting the externally acquired *oqx* and *qnr* genes, it did not evaluate mutations in the quinolone resistance-determining regions (QRDR) of the *gyrA* and *parC* genes that are the inhibitory targets of quinolones. While the frequency of external acquisition has at least declined and might be approaching a desirable situation, further ongoing surveillance is essential. As the research group's metagenomic analysis technique conforms to metagenomic analysis techniques used globally, the study is believed to have provided information that will be important when comparing reports from different countries. In order to cover every wastewater treatment facility in all prefectures, development of metagenomic analysis methods that offer even better cost effectiveness should be promoted. The group plans to continue conducting nationwide surveillance twice a year (in summer and winter) with the assistance of local governments and put in place Japanese environmental AMR (resistome) infrastructure.

In addition to ARG in wastewater, it is vital to identify the presence of ARB that could potentially exist and proliferate in the environment. Information on the situation within Japan is starting to emerge from the findings of the aforementioned MHLW research group, including reports that, at a water reclamation center in Tokyo Bay, a KPC-2-producing *Klebsiella pneumoniae (Sequence type 11: ST11)* strain rarely found in Japan, even in clinical isolates, has been isolated, that ST11 was the same type as clinical isolates widely isolated in East Asia [3], that KPC-2 was found in *Aeromonas* rarely isolated in wound infections,[4] and that *E. coli* with NDM- 5 carbapenemase, which has acquired broader-spectrum activity than NDM-1, has been isolated.[5] A report has also been published on a comprehensive AMR study carried out on hospital wastewater, inlet and outlet water from sewage treatment plants, and river water in the Yodo River basin in Osaka. Its estimates suggest that a diverse array of ARB will be isolated from outlet water from sewage treatment plants and that hospital wastewater will impose an environmental AMR burden unless ozone treatment is carried out.[6] As in the case of the contamination situation overseas, a more extensive field survey would appear to be required in Japan, at least to ascertain the true extent of the isolation of ARB in environmental water, and it will be crucial to develop techniques for intensively eliminating or reducing ARB alone.

Thus, establishing surveillance techniques for monitoring environmental AMR and residual antimicrobials, and actually conducting fact-finding studies are important. As a method for investigating drug resistance in environmental water, a procedure for metagenomic analysis of treated effluent from sewage treatment plants was developed. Conventional culture methods were also important, and not only the detection of genes, but also the analysis of the characteristics of live resistant bacteria in sewage was conducted. It is hoped that conducting both the metagenomic analysis and the culture method approaches will lead to a better understanding of the overall picture of drug resistance in environmental waters. In addition to a nationwide environmental water AMR survey, the study also includes a survey of the status of environmental AMR of local hospital effluent and the sewage from a local pig farm, and an analysis of antimicrobials in local sewage treatment water in Japan. Risk assessment should be based on these findings and a literature review on environmental AMR. To set out the evidence concerning environmental AMR from overseas, the research group published a translation of Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges (2018).

Important issues for environmental AMR control include: 1) the environment can be contaminated with antimicrobial agents and resistant bacteria if wastes are not appropriately treated; 2) the impact of environmental contamination with antimicrobial agents and resistant bacteria in wastes on human health is not well understood; 3) to understand the risk of resistant bacteria to human health, it is important to assess where and how many resistant bacteria are present in environmental water; and 4) evaluate sampling and testing methods and standardize practices to measure resistant bacteria in environmental water.

A Japanese literature review reported that a considerable amount of resistant bacteria and resistant genes remain in effluent water after treatment and in the river water that receives it, placing a concern for the environmental contamination; resistant bacteria (such as KPC-2 and NDM-5-producing bacteria), which are rarely isolated clinically in Japan, have been detected in sewage, suggesting that sewage is useful for monitoring drug resistance in the city. Although the existence of drug resistance in the environment has been proven in Japan and overseas, there is insufficient evidence on the risks to humans and animals due to the lack of established survey methods and assessment criteria for environmental AMR.

A literature review was conducted on sewage AMRs in Japan.[8] Of 37 eligible papers from 1991-2021, 26 were AMRs, 10 were antimicrobial agents and one was both an AMR and an antimicrobial agent. The presence of clinically important ARBs, ARGs and residual antimicrobials such as ESBL-producing bacteria, CRE, MDRP, MDRA, MRSA and VRE in Japanese sewage was observed. Hospital drainage may be a reservoir of clinically important ARBs, but the direct risk to humans of ARBs in hospital drainage is not clear. In addition, antimicrobials commonly used in Japan may contribute to the selection and spread of AMR in sewage. While promotion of AMR control in humans, animals and the environment is necessary, knowledge on AMR in the environment is still limited compared to humans and animals. Progress in surveys and research on environmental AMR in Japan is anticipated.

Although efforts have been made to assess the risk of infection transmission and the health effects in cases of nosocomial infection based on the results of field epidemiology and molecular epidemiological analysis of isolates, as described above, research findings indicating that antimicrobial-resistant bacteria derived from the environment affect human and animal health are scarce. Overseas, as the contamination of vegetables believed to result from the use of river water for irrigation [9] and assessments of the risk of exposure through water-based recreation [10] are starting to be reported, albeit only little by little, the risk cycle is being calculated to a certain degree. At this point, it is difficult to set definite standards for discussing environmental risk. However, it is vital to quantitatively monitor and evaluate environmental AMR, conduct research that could assist in appraising health risks, and undertake risk assessments and reviews of major literature from both within Japan and overseas, as shedding light on the major factors contributing to the environmental AMR load and investigating whether it is developing into a risk to human and animal health are matters of urgency. A multidisciplinary One Health approach at the human-animal-environment interface to infectious diseases is essential to assess the risk to humans and animals of agent resistance in the environment.[11]

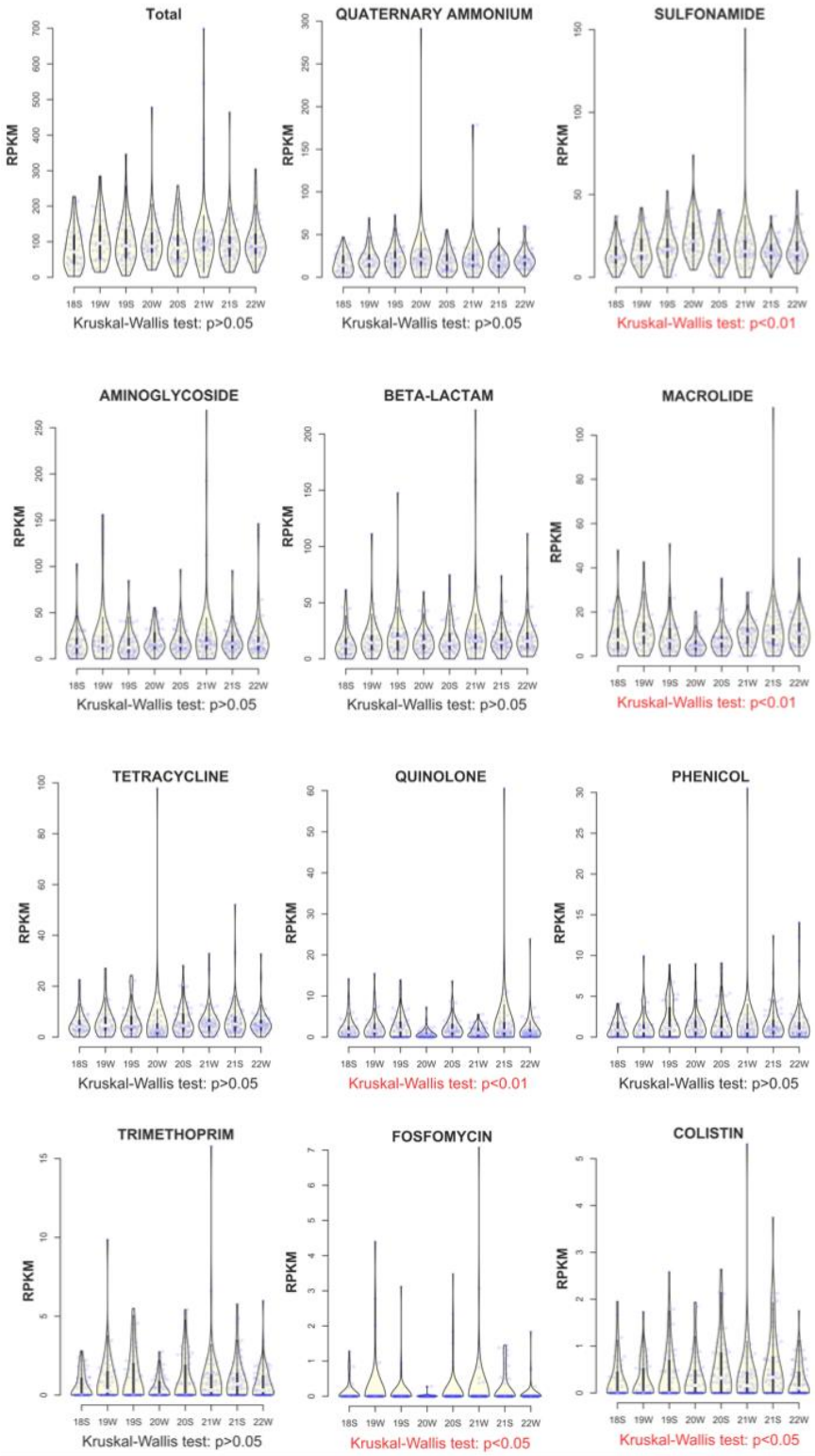

Figure 3. Metagenomic analysis (Metagenomic DNA-Seq) of wastewater discharged from Japanese sewage treatment plants (water reclamation centers) The quantity of antimicrobial resistant genes (ARGs) in each category detected in treated effluent provided by local governments during the eight survey periods from summer in 2018 (18S) to winter in 2022 (22W) was standardized using Reads Per Kilobase of gene per Million mapped reads (RPKM).

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7. Current Volume of Use of Antimicrobials in Japan

(1) Antimicrobials for humans

1) Usage of antimicrobials in Japan

Source: Japan Surveillance of Antimicrobial Consumption (JSAC)

Antimicrobial use based on sales volume in Japan from 2013 to 2021 is shown in Table 72 (oral agents), Table 73 (injectable agents), and Table 74 (total of oral and injectable antimicrobial agents). Overall use of antimicrobials in Japan in 2020 amounted to 10.18 DID. A comparison with DID in major countries in 2020 shows that this was lower than France (20.3 DID), Italy (18.4 DID), and the Sweden (10.4 DID), but higher than Germany (8.9 DID), and the Netherlands (8.5 DID) [1]. Looking at changes over time, no significant changes in antimicrobial use were observed from 2013 to 2016, but the decline began in 2017, with the decrease becoming smaller. In the midst of such a trend, there was an epidemic of COVID-19 infections, and overall antimicrobial use in 2020 declined more sharply compared to the previous years. The same trend continued in 2021 with 9.8 DID showing a 32.7% decrease compared to 2013.

Oral antimicrobial use in 2021 (Table 72) was 8.9 DID (90.9%). Antimicrobials subject to a reduction target of 50% under Japan's National Action Plan on AMR, namely oral cephalosporins (2.1 DID), oral fluoroquinolones (1.5DID), and oral macrolides (2.7 DID) together accounted for 71.1% of all oral antimicrobials (the figure for oral cephalosporins is the total for first- (0.1 DID), second- (0.3 DID), and third-generation (1.7 DID) oral cephalosporins). While this trend has not changed since 2013, use of oral cephalosporins, oral fluoroquinolones, and oral macrolides fell by 46.1%, 43.7%, and 47.5% respectively over that period. The use of parenteral antimicrobials decreased by 1.1% between 2013 and 2020 (Table 73). The use of parenteral antimicrobials remained flat with no decline until 2019, possibly due to the increase in the elderly population, which may have increased the opportunity to use parenteral antimicrobials. It was also thought that 2019 may have seen a decrease in first-generation cephalosporins and an increase in narrow-range penicillins, penicillin with be-lactamase inhibitors, second- and third-generation cephalosporins, and carbapenems, especially due to cephazolin supply shortage issues. [2] Overall antimicrobial use decreased scince 2020, which may be due not only to the promotion of appropriate antimicrobial use, but also to the impact of COVID-19 (e.g., fewer patients seen with infections other than new coronavirus infections). A similar trend was seen to continue in 2021 due to the continuing pandemic.

Table 75 shows antimicrobial use based on the AWaRe classification recommended by the WHO as an indicator of antimicrobial stewardship. Carried in the 20th edition of the WHO Model Lists of Essential Medicines, the AWaRe classification is an antimicrobial classification system that is applied as an indicator of antimicrobial stewardship. It classifies antimicrobials into four categories: Access (first- or second-choice antimicrobials used for treating common infections, regarding whose resistance potential there is little concern, and which should be made widely available by all countries in high-quality formulations at a reasonable cost. Examples include ampicillin and cephalexin), Watch (antimicrobials that should be used only for a limited number of conditions or applications, as their resistance potential is a source of concern. Examples include vancomycin, meropenem, levofloxacin, and ceftriaxone), Reserve (antimicrobials that should be used as the last resort when no other alternatives can be used. Examples include tigecycline, colistin, and daptomycin), and Unclassified. This classification was amended in 2019 to add the new category of "discouraged antibiotics," consisting of antimicrobials whose clinical use the WHO does not recommend (for example, cefoperazone-sulbactam). The WHO has set a target of at least 60% of antimicrobial consumption being from medicines in the Access Group. While consumption of antimicrobials in the Access Group as a proportion of total use is lower in Japan than other countries,[3] the figure has risen gradually over the years since 2013 from 11.0% to 23.1% in 2021, with the percentage of antimicrobials in the Watch Group falling from 87.5% to 75.5%, which can mean that Japan is on its way to meeting the AWaRe classification recommendation.

However, various factors, such as the problem of antimicrobial supply shortages and the impact of new coronavirus infections, are also of concern and require continued close monitoring.

A survey of oral and parenteral antimicrobial use in terms of potency by weight from a One Health perspective (Table 76) also confirmed a decrease in overall use as well. The decrease in the use of oral third generation cephalosporins, fluoroquinolones, and macrolides accounted for half of the total, and it is necessary to clarify the factors from the viewpoint of proper use, including the impact of COVID-19 infection. Since there may be a temporary decline, it is important to carefully monitor future trends in antimicrobial use on an ongoing basis.

The establishment of a surveillance system, which was one of the goals of the Action Plan for AMR control, made it possible to assess the use of antimicrobial agents in Japan over time. Although the impact of AMR control was recognized in the gradual decline of oral agents through 2019, parenteral antimicrobial agents remained flat to increased, which was thought to be due to factors such as an increase in the elderly population. In 2020, however, oral agents declined further, and parenteral antimicrobial agents also began to decline. One reason for the decrease may be the various effects associated with new coronavirus infections, and it is necessary to understand future trends. Furthermore, it is important to clarify the purpose of antimicrobial use and evaluate appropriateness by continuing surveillance of antimicrobial use based not only on sales volume data but also on National Database for Prescription and National Health Checkups (NDB).

Table 73. Trends in oral antimicrobial use in Japan based on the volume of sales

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Tetracyclines	0.76	0.75	0.77	0.80	0.81	0.88	0.96	1.10	1.18
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Penicillins with extended spectrum	0.60	0.61	0.68	0.66	0.65	0.69	0.77	0.61	0.59
Beta Lactamase-sensitive penicillins	0.01	0.01	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Combinations of penicillins, including beta lactamase inhibitors	0.15	0.16	0.17	0.18	0.19	0.20	0.23	0.18	0.19
1st generation cephalosporins	0.07	0.07	0.07	0.07	0.07	0.08	0.09	0.09	0.10
2nd generation cephalosporins	0.30	0.30	0.29	0.29	0.28	0.28	0.30	0.29	0.31
3rd generation cephalosporins	3.54	3.41	3.46	3.32	3.08	2.83	2.63	1.85	1.70
Carbapenems	0.01	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01
Other cephalosporins and penems	0.14	0.14	0.13	0.12	0.12	0.11	0.10	0.09	0.09
Combinations of sulfonamides and trimethoprim, including derivatives	0.25	0.27	0.29	0.31	0.33	0.36	0.38	0.41	0.44
Macrolides	4.83	4.50	4.59	4.56	4.18	3.96	3.84	2.93	2.72
Lincosamides	0.01	0.01	0.02	0.01	0.02	0.02	0.02	0.02	0.02
Fluoroquinolones	2.83	2.83	2.71	2.75	2.57	2.42	2.32	1.66	1.48
Other quinolones	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.10	0.10	0.10	0.10	0.09	0.08	0.08	0.06	0.06
Total	13.62	13.18	13.30	13.19	12.38	11.92	11.74	9.31	8.88

* As a unit, DIDs (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2022.

Table 74. Trends in parenteral antimicrobial use in Japan based on the volume of sales

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Tetracyclines	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Penicillins with extended spectrum	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Beta-lactamase sensitive penicillins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Combinations of penicillins, incl. beta-lactamase inhibitors	0.13	0.15	0.16	0.18	0.19	0.21	0.22	0.18	0.20
First-generation cephalosporins	0.13	0.13	0.14	0.14	0.15	0.15	0.12	0.13	0.14
Second-generation cephalosporins	0.11	0.11	0.10	0.10	0.10	0.09	0.10	0.08	0.08
Third-generation cephalosporins	0.18	0.19	0.21	0.22	0.23	0.24	0.27	0.22	0.21
Fourth-generation cephalosporins	0.04	0.03	0.03	0.03	0.03	0.03	0.02	0.02	0.02
Monobactams	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Carbapenems	0.09	0.08	0.08	0.08	0.08	0.08	0.08	0.07	0.07
Other cephalosporins and penems	-	-	-	-	-	-	<0.01	<0.01	<0.01
Combinations of sulfonamides and trimethoprim, incl. derivatives	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Macrolides	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Lincosamides	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.01
Streptogramins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	-	-
Streptomycins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other aminoglycosides	0.05	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.02
Fluoroquinolones	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.03	0.03
Glycopeptide antibacterials	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Polymyxins	-	-	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Metronidazole	-	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.01
Total	0.90	0.90	0.94	0.96	0.98	0.99	1.01	0.87	0.89

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2022.

Table 75. Trends in oral and parenteral antimicrobial use in Japan based on sales volume

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Tetracyclines	0.79	0.77	0.79	0.82	0.83	0.90	0.98	1.12	1.19
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Penicillins with extended spectrum	0.63	0.64	0.70	0.68	0.67	0.71	0.79	0.63	0.61
Beta-lactamase sensitive penicillins	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	<0.01
Combinations of penicillins, incl. beta-lactamase inhibitors	0.29	0.31	0.34	0.36	0.38	0.41	0.45	0.36	0.38
First-generation cephalosporins	0.20	0.20	0.20	0.21	0.22	0.23	0.21	0.22	0.24
Second-generation cephalosporins	0.41	0.40	0.39	0.39	0.37	0.38	0.41	0.38	0.39
Third generation cephalosporins	3.72	3.60	3.67	3.54	3.31	3.07	2.90	2.07	1.91
Fourth generation cephalosporins	0.04	0.03	0.03	0.03	0.03	0.03	0.02	0.02	0.02
Monobactams	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Carbapenems	0.10	0.10	0.10	0.10	0.09	0.09	0.09	0.07	0.08
Other cephalosporins and penems	0.14	0.14	0.13	0.12	0.12	0.11	0.10	0.09	0.09
Combinations of sulfonamides and trimethoprim, incl. derivatives	0.25	0.27	0.29	0.32	0.34	0.36	0.39	0.41	0.44
Macrolides	4.84	4.51	4.59	4.56	4.18	3.96	3.84	2.93	2.73
Lincosamides	0.04	0.04	0.04	0.04	0.03	0.03	0.04	0.03	0.03
Streptogramins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	-	-
streptomycins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other aminoglycosides	0.05	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.02
Fluoroquinolones	2.86	2.86	2.74	2.78	2.60	2.45	2.35	1.68	1.51
Other quinolones	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Glycopeptide antibacterials	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Polymyxins	-	-	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Metronidazole	-	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.12	0.12	0.12	0.12	0.10	0.10	0.10	0.08	0.07
Total	14.52	14.08	14.23	14.15	13.36	12.91	12.75	10.18	9.77

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2022.

Table 76. Trends in antimicrobial use in Japan by AWaRe classification

AWaRe Classification	2013	2014	2015	2016	2017	2018	2019	2020	2021
Access (%)	1.60	1.64	1.76	1.81	1.87	2.03	2.22	2.15	2.26
	(10.99)	(11.66)	(12.34)	(12.78)	(14.03)	(15.76)	(17.42)	(21.09)	(23.12)
Watch (%)	12.71	12.23	12.28	12.15	11.30	10.70	10.36	7.78	7.38
	(87.57)	(86.90)	(86.25)	(85.86)	(84.62)	(82.89)	(81.27)	(77.48)	(75.49)
Reserve (%)	0.18	0.18	0.18	0.17	0.16	0.15	0.15	0.13	0.12
	(1.27)	(1.28)	(1.24)	(1.20)	(1.18)	(1.16)	(1.15)	(1.26)	(1.23)
Non-recommended (%)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
	(0.16)	(0.16)	(0.16)	(0.15)	(0.16)	(0.16)	(0.16)	(0.17)	(0.17)
Unclassified (%)	0.00	0.00	0.00	0.00	0.00	0.00	-	-	-
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.00)	-	-	-
Total	14.52	14.08	14.23	14.15	13.36	12.91	12.75	10.18	9.77

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2022. AWaRe classification 2021 edition was used.

Table 77. Antimicrobial consumption by weight based on sales volume in Japan, converted to potency (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Tetracyclines	7.1	6.9	7.1	7.2	7.0	7.3	7.7	8.4	8.7
Amphenicols	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Penicillins with extended spectrum	53.7	53.6	57.6	56.3	54.5	57.3	62.6	49.3	47.9
Beta Lactamase-sensitive penicillins	1.7	1.8	1.7	1.5	1.4	1.3	1.8	1.3	1.1
Combinations of penicillins, including beta lactamase inhibitors	88.4	95.7	106.1	114.9	124.4	132.2	146.0	118.0	129.2
1st generation cephalosporins	25.0	24.9	25.2	26.3	27.2	28.4	24.9	26.5	28.9
2nd generation cephalosporins	28.5	27.4	27.0	26.7	25.9	26.0	28.6	25.5	26.5
3rd generation cephalosporins	97.7	95.1	97.8	95.9	91.2	86.6	85.3	64.0	59.8
4th generation cephalosporins	6.6	6.1	6.0	5.7	5.5	4.8	4.5	4.3	4.2
Monobactams	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbapenems	9.9	9.9	10.1	10.2	10.1	9.8	10.0	8.8	9.1
Other cephalosporins and penems	4.8	4.7	4.6	4.3	4.0	3.8	3.6	3.3	3.0
Combinations of sulfonamides and trimethoprim including derivatives	45.8	49.9	53.7	58.6	62.1	65.7	71.0	75.7	81.3
Macrolides	108.0	101.4	103.4	102.9	94.5	89.7	87.2	67.8	63.4
Lincosamides	2.8	2.7	2.6	2.5	2.4	2.4	2.7	2.1	2.1
Streptogramins	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	—	—
Streptomycin	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Other aminoglycosides	1.0	0.9	0.9	0.8	0.8	0.7	0.7	0.5	0.5
Fluoroquinolones	61.3	60.2	56.6	57.4	53.2	50.1	47.7	33.0	29.2
Other quinolones	0.5	0.4	0.3	0.3	0.2	0.1	0.1	0.1	<0.1
Glycopeptides	2.2	2.1	2.3	2.4	2.5	2.4	2.6	2.7	2.4
Polymyxins	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Metronidazole (parenteral)	<0.1	<0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Other antibacterials	17.5	16.5	16.6	16.7	14.3	13.8	13.1	10.3	9.3
TOTAL	563.0	560.6	580.1	591.4	581.6	582.9	600.2	501.9	507.0

Table 78. Trends in the use of total oral and parenteral antimicrobial agents in Japan based on NDB

	2013	2014	2015	2016	2017	2018	2019	2020
Tetracyclines	0.75	0.74	0.75	0.78	0.79	0.85	0.93	1.06
Amphenicols	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Penicillins with extended spectrum	0.53	0.56	0.64	0.64	0.63	0.67	0.76	0.61
Beta-lactamase sensitive penicillins	0.01	0.01	0.01	0.01	0.00	0.00	0.01	0.01
Combinations of penicillins, incl. beta-lactamase inhibitors	0.25	0.27	0.29	0.31	0.33	0.35	0.38	0.31
First-generation cephalosporins	0.14	0.15	0.16	0.16	0.17	0.18	0.17	0.19
Second-generation cephalosporins	0.34	0.35	0.36	0.35	0.34	0.34	0.37	0.35
Third generation cephalosporins	3.47	3.54	3.69	3.57	3.34	3.11	2.94	2.10
Fourth generation cephalosporins	0.03	0.03	0.03	0.03	0.02	0.02	0.02	0.02
Monobactams	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Carbapenems	0.08	0.08	0.08	0.08	0.08	0.07	0.07	0.06
Other cephalosporins and penems	0.12	0.12	0.12	0.11	0.11	0.10	0.10	0.09
Combinations of sulfonamides and trimethoprim, incl. derivatives	0.23	0.25	0.27	0.29	0.31	0.33	0.36	0.38
Macrolides	4.97	4.93	5.07	5.03	4.64	4.44	4.37	3.30
Lincosamides	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Streptogramins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
streptomycins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other aminoglycosides	0.05	0.05	0.05	0.04	0.04	0.03	0.03	0.02
Fluoroquinolones	2.78	2.74	2.93	2.93	2.74	2.61	2.51	1.78
Other quinolones	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Glycopeptide antibacterials	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.03
Polymyxins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Metronidazole	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other antibacterial agents	0.11	0.11	0.11	0.11	0.09	0.09	0.09	0.07
Total	13.93	13.99	14.63	14.51	13.70	13.28	13.15	10.41

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2021.

2) Usage of parenteral antimicrobials in hospitals

Source: J-SIPHE

J-SIPHE, operated by AMRCRC, uses an integrated inpatient EF file* to survey antimicrobial use in participating facilities and publishes the annual reports.[5] In 2020, overall in-hospital use of intravenous antimicrobial agents were on increase compared to the previous year. Penicillins (AUD 3.92, DOT 5.77) were the most commonly used, followed by 3rd generation cephalosporins (AUD 2.91, DOT 4.02), 1st generation cephalosporins (AUD 2.52, DOT 3.40), and carbapenems (AUD 1.12, DOT 2.04). It is necessary to continuous monitor the trend in the future.

*E-file: Medical billing data; F-file: "Receipt" file for inpatients with procedure statement information integrated

Table 79. Use of parenteral antimicrobials at medical institutions (AUD, DOT)

	2019		2020		2021	
	AUD (IQR) (DDDs/100 patient-days)	DOT (IQR) (DOTs/100 patient-days)	AUD (IQR) (DDDs/100 patient-days)	DOT (IQR) (DOTs/100 patient-days)	AUD (IQR) (DDDs/100 patient-days)	DOT (IQR) (DOTs/100 patient-days)
Penicillin	3.90(2.71-5.10)	5.94(4.15-7.82)	3.48(2.15-4.82)	5.19(3.53-7.01)	3.92 (2.32-5.32)	5.77 (3.7-7.35)
1st generation cephalosporins	1.71(0.83-2.86)	2.23(1.21-3.94)	2.28(1.15-3.27)	3.11(1.58-4.36)	2.52 (1.22-3.62)	3.40 (1.72-4.73)
2nd generation cephalosporins	0.18(0.09-0.41)	0.37(0.19-0.83)	0.15(0.06-0.35)	0.29(0.13-0.69)	0.14 (0.06-0.29)	0.27 (0.12-0.60)
3rd generation cephalosporins	3.33(2.18-4.74)	4.58(3.05-6.30)	3.00(1.95-4.32)	4.04(2.87-5.60)	2.91 (1.90-4.32)	4.02 (2.68-5.42)
4th generation cephalosporins	0.34(0.14-0.70)	0.53(0.25-1.01)	0.31(0.14-0.76)	0.49(0.26-1.05)	0.32 (0.16-0.74)	0.55 (0.28-1.02)
Oxacefemmes	0.30(0.11-0.70)	0.31(0.12-0.76)	0.25(0.11-0.61)	0.27(0.11-0.64)	0.20 (0.09-0.54)	0.20 (0.10-0.55)
Cephamycins	0.89(0.52-1.41)	1.70(0.99-2.62)	0.91(0.47-1.42)	1.67(0.93-2.62)	1.01 (0.53-1.52)	1.87 (1.04-2.76)
Ceftorozan/Tazobactam	0.06(0.03-0.10)	0.07(0.03-0.11)	0.09(0.06-0.14)	0.09(0.06-0.13)	0.00(0.00-0.00)	0.00(0.00-0.00)
Carbapenems	1.23(0.63-1.79)	2.05(1.15-3.00)	1.09(0.55-1.87)	1.95(1.04-2.90)	1.12 (0.56-1.91)	2.04 (1.09-3.05)
Monobactams	0.04(0.02-0.09)	0.07(0.03-0.11)	0.04(0.02-0.09)	0.07(0.04-0.10)	0.05 (0.03-0.07)	0.07 (0.05-0.11)
Glycopeptides	0.56(0.27-0.94)	0.81(0.46-1.32)	0.48(0.25-0.92)	0.77(0.40-1.30)	0.50 (0.26-0.95)	0.77 (0.43-1.32)
Oxazolidinones	0.11(0.07-0.16)	0.11(0.07-0.17)	0.11(0.07-0.18)	0.12(0.08-0.20)	0.12 (0.07-0.19)	0.13 (0.08-0.21)
Arbekacine	0.07(0.04-0.13)	0.07(0.04-0.12)	0.08(0.04-0.14)	0.08(0.04-0.15)	0.08 (0.04-0.16)	0.08 (0.04-0.16)
Daptomycin	0.25(0.14-0.38)	0.17(0.11-0.28)	0.24(0.14-0.39)	0.16(0.11-0.26)	0.26 (0.15-0.44)	0.18 (0.11-0.30)
Quinolones	0.39(0.21-0.61)	0.41(0.23-0.64)	0.37(0.22-0.59)	0.40(0.25-0.63)	0.35 (0.22-0.59)	0.38 (0.24-0.63)
Aminoglycosides	0.10(0.06-0.18)	0.23(0.14-0.45)	0.10(0.05-0.17)	0.24(0.14-0.43)	0.10 (0.05-0.20)	0.25 (0.15-0.49)
Tetracyclines	0.14(0.09-0.26)	0.17(0.10-0.29)	0.15(0.09-0.27)	0.17(0.10-0.33)	0.15 (0.09-0.30)	0.17 (0.10-0.32)
Lincomycins	0.22(0.13-0.39)	0.32(0.19-0.55)	0.20(0.13-0.33)	0.28(0.18-0.46)	0.19 (0.12-0.32)	0.27 (0.18-0.43)
Macrolides	0.07(0.04-0.10)	0.07(0.04-0.10)	0.07(0.05-0.11)	0.07(0.05-0.12)	0.07 (0.04-0.11)	0.07 (0.05-0.11)
Sulfamethoxazole/Trimethoprim	0.07(0.03-0.11)	0.06(0.03-0.09)	0.07(0.03-0.14)	0.06(0.03-0.11)	0.08 (0.04-0.14)	0.07 (0.04-0.11)
Metronidazole	0.10(0.07-0.17)	0.11(0.07-0.18)	0.11(0.06-0.17)	0.12(0.07-0.19)	0.12 (0.08-0.18)	0.14 (0.09-0.21)

AUD: Antimicrobial Use Density, DOT: Days of Therapy

* Note: Ceftorozan/Tazobactam was not used in 2021 due to supply disruption

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5. J-SIPHE Annual Report 2019, 2020

(2) Veterinary agents

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Based on the volumes of sales of antibiotics and synthesized antimicrobials, as reported under the Veterinary Agent Control Regulations, the amounts of veterinary antimicrobials were calculated in terms of active ingredients (metric tons (t)). In the period from 2013 to 2020 the volume of sales of veterinary antimicrobials ranged between 748.44 to 858.09 t. The total volume of sales in 2020 was largely unchanged, increased by approx. 1.6 t since 2019. Sulfonamides increased by about 14 t, followed by penicillins by about 5 t. The increase in sulfonamides was mainly due to cattle and poultry. In contrast, the decrease was observed in tetracyclines (approx. 9 t) and macrolides (approx. 7 t), with a particularly significant impact on swine for tetracyclines and on aquatic animals (seawater fish) for macrolides. Tetracyclines represented the largest share of antimicrobial sales over the period monitored, accounting for between 36.1% and 43.7%.

On the other hand, third-generation cephalosporins and fluoroquinolones, which are important antimicrobials for human medicine, accounted for less than 1% of overall volume of sales.

Table 80. Amounts of veterinary antimicrobials in terms of active ingredients by class (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Penicillins	78.17	77.96	83.73	90.01	88.08	88.99	92.41	96.97
Cephalosporins(total)	5.58	5.50	5.89	6.45	6.65	7.06	8.02	7.72
1st generation cephalosporins	(4.71)	(4.58)	(4.98)	(5.41)	(5.50)	(5.67)	(6.62)	(6.40)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)	(0.18)	(0.22)	(0.14)	(0.15)
3rd generation cephalosporins	(0.68)	(0.71)	(0.79)	(0.88)	(0.96)	(1.18)	(1.26)	(1.16)
Aminoglycosides	39.52	40.64	35.47	47.86	44.76	35.61	35.17	36.89
Macrolides	77.70	70.43	98.41	134.12	140.83	154.72	180.71	173.72
Lincosamides	38.99	43.26	28.66	21.87	25.26	22.76	21.29	21.45
Tetracyclines	340.52	324.85	333.86	331.55	347.05	311.18	313.03	304.38
Peptides	11.78	9.98	14.54	14.02	19.99	12.34	19.56	19.06
Other antibioitics	25.98	28.85	32.39	31.96	36.19	37.50	35.96	36.34
Sulfonamides	103.90	97.57	96.67	95.85	99.06	88.77	84.69	98.53
Quinolones	1.01	1.91	1.71	1.74	1.84	1.48	2.57	2.34
Fluoroquinolones	5.53	5.63	7.35	6.08	6.83	6.65	7.53	7.06
Amphenicols	21.53	26.15	29.73	26.49	27.11	24.82	27.38	25.55
Furan and derivatives	14.46	1.76	1.24	1.57	1.36	1.34	1.35	1.23
Other synthetic antibacterials	15.02	13.97	13.35	12.12	13.09	11.98	11.71	11.68
Total	779.70	748.44	782.98	821.70	858.09	805.19	841.37	842.92

* The figures in parentheses are included in the Cephalosporins (total).

The marketing authorization holders also submit the percentage of sales for each species of domestic animal estimated from information on the distributors, so the estimated volumes for each species sold are calculated based on those estimated percentages. In terms of active ingredients, swine accounted for the largest amount, followed by seawater fish. Since 2019, sales have decreased in swine, while they increased in beef and dairy cattle. The reasons for those fluctuations are not clear, but it was considered possible that the increase in beef and dairy cattle may have been due to an increase in pneumonia and other diseases, while the decrease in swine may have been due to increased awareness of the need for prudent use and improved biosecurity measures due to the outbreak of classical swine fever.

In order to conduct comparisons of usage by animal species, the number of heads and weight per head of the animal should be taken into account. Accordingly, there is a comparison method which involves using animal weights and numbers to calculate biomass weight (total weight of animals) and expressing figures for antimicrobial use as usage per unit of biomass weight. The WOAH has recently set out a method for calculating biomass weight as part of its collection of veterinary antimicrobial usage data.[14] The standard weights for each animal type are calculated on a regional basis and, as the figures have not been published as yet and could vary from year to year, it is not possible to conduct an evaluation using Japanese data alone. The biomass weight for the country calculated by the WOAH will be provided to each country for the data to be collected from 2022 onwards, which will enable comparisons with other regions of the world based on the consistent methodology.

Table 81. Estimated amounts of veterinary antimicrobials in terms of active ingredients by animal species (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Beef cattle	23.02	20.35	23.77	25.00	25.92	33.17	33.40	58.33
Dairy cow	31.73	30.45	32.48	35.10	34.55	41.01	36.79	48.71
Horse	2.18	2.01	2.10	2.31	2.17	3.90	3.49	3.84
Swine	502.64	490.42	503.13	513.86	541.61	471.36	450.24	421.27
Broiler	65.90	70.14	62.36	63.81	61.74	62.79	69.81	77.53
Layer	23.29	23.67	19.36	19.78	15.32	15.86	17.56	17.13
Fish (seawater)	112.36	93.41	123.02	143.03	159.07	164.00	217.66	204.15
Fish (freshwater)	6.84	5.61	7.28	10.10	9.07	2.91	2.74	2.27
Ornamental fish	0.72	1.07	1.60	1.95	1.74	1.63	1.64	1.56
Dog/Cat	8.49	8.10	7.78	6.67	6.90	8.56	8.03	8.11
Other	2.54	3.22	0.09	0.10	0.00	0.00	0.00	0.00
Total	779.70	748.44	782.96	821.70	858.09	805.19	841.37	842.92

1) Food-producing animals

The estimated volumes of veterinary antimicrobials sold for food-producing animals (cattle, swine, horses, chickens, and others) in terms of active ingredients are listed in Table 82. In the period from 2013 to 2020, the estimated volume of sales ranged between 611.29 t and 681.31 t. The volume of sales in 2020 was the second lowest since 2013, but has increased by approximately 16 t since 2019, when the volume of sales was the lowest since 2013. This was mainly due to an increase in sulfonamides (approx. 16 t), which increased in cattle and poultry. While tetracyclines (240.12 t to 286.74 t) have been taking up the largest share in the overall volume of sales of antimicrobials for food-producing animals, accounting for 38.3 to 44.0%, their volume and share in 2020 were at the lowest with 240.12 t and 38.3%, respectively, since 2013. This was caused by decreased use in swine. In contrast, third-generation cephalosporins and fluoroquinolones, which are critically important antimicrobials for human medicine, each accounted for 0.1% and 1% of the antimicrobial agents for livestock animals, respectively

Table 82. The estimated volumes of sales of veterinary antimicrobials for food-producing animals (cattle, swine, horses, chickens, and others) in terms of active ingredients (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Penicillins	59.50	61.96	67.25	73.82	71.75	74.48	73.76	76.22
Cephalosporins (total)	3.12	3.06	3.22	3.34	3.44	3.91	4.11	3.79
1st generation cephalosporins	(2.45)	(2.34)	(2.52)	(2.52)	(2.51)	(2.73)	(2.93)	(2.68)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)	(0.18)	(0.22)	(0.14)	(0.15)
3rd generation cephalosporins	(0.49)	(0.51)	(0.58)	(0.65)	(0.74)	(0.96)	(1.04)	(0.95)
Aminoglycosides	37.40	38.66	34.07	47.46	44.37	34.69	34.77	36.52
Macrolides	56.00	53.30	60.36	72.68	71.96	72.09	73.29	72.71
Lincosamides	35.88	36.61	23.65	15.62	19.39	16.72	16.26	17.48
Tetracyclines	286.74	275.83	276.24	280.66	286.01	257.36	242.93	240.12
Peptides	11.77	9.97	14.54	14.01	19.98	12.34	19.56	19.05
Other antibioitics	25.71	28.43	32.23	31.55	35.72	36.87	35.64	35.54
Sulfonamides	95.62	88.43	84.40	78.57	84.10	78.59	68.64	84.38
Quinolones	0.22	0.20	0.20	0.16	0.31	0.01	0.11	0.18
Fluoroquinolones	4.64	4.73	6.41	5.19	5.93	5.80	6.66	6.18
Amphenicols	19.66	25.14	27.39	24.82	25.34	23.28	23.89	23.11
Furan and derivatives	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other synthetic antibacterials	14.98	13.92	13.32	12.07	13.02	11.96	11.68	11.53
Total	651.24	640.25	643.28	659.95	681.31	628.09	611.29	626.83

* The figures in parentheses are included in the Cephalosporins (total).

2) Aquatic animals

The estimated volumes of veterinary antimicrobials sold for aquatic animals (seawater fish, freshwater fish, and ornamental fish) in terms of active ingredients are summarized in Table 83. In the period from 2013 to 2020, the estimated volume of sales ranged between 100.09 t to 222.05 t, accounting for between 13.4% and 26.4% of the total volume of veterinary antimicrobial sales. Tetracyclines took up the largest share in the overall volume of sales until 2015 but it has changed to a macrolide (erythromycin) since 2016. The approximately 88 t increase in the volume of sales between 2013 and 2020 was due to a rise in sales of a macrolide (erythromycin), which was presumably attributed to an outbreak and treatment of infections caused by *Lactococcus garvieae* (type II alpha-hemolytic streptococcal disease) different to the conventional serotypes.

Third-generation cephalosporins and fluoroquinolones that are important for human health are not approved for aquatic animal use.

Table 83. The estimated volumes of sales of veterinary antimicrobials for aquatic animals (seawater fish, freshwater fish, and ornamental fish) in terms of active ingredients (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Penicillins	16.31	13.87	14.38	14.62	14.66	12.85	17.01	19.21
Cephalosporins (total)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1st generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2nd generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3rd generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Aminoglycosides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Macrolides	21.70	17.13	38.05	61.44	68.87	82.61	107.40	101.01
Lincosamides	3.02	6.56	4.90	6.12	5.73	5.91	4.88	3.82
Tetracyclines	53.78	49.01	57.62	50.89	61.05	52.55	69.57	63.84
Peptides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other antibioitics	0.27	0.42	0.16	0.42	0.47	0.63	0.32	0.80
Sulfonamides	7.68	8.59	11.71	16.74	14.39	9.64	15.56	13.36
Quinolones	0.79	1.71	1.51	1.58	1.53	1.47	2.45	2.15
Fluoroquinolones	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Amphenicols	1.87	1.01	2.33	1.67	1.77	1.53	3.48	2.43
Furan and derivatives	14.46	1.76	1.24	1.57	1.36	1.34	1.35	1.23
Other synthetic antibacterials	0.02	0.04	0.02	0.04	0.06	0.02	0.02	0.12
Total	119.91	100.09	131.91	155.08	169.88	168.54	222.05	207.98

3) Companion animals

The estimated volumes of veterinary antimicrobials sold for companion animals (dogs and cats) in terms of active ingredients are summarized in Table 84. In the period from 2013 to 2020, the estimated volume of sales ranged between 6.67 to 8.56 t, accounting for between 0.8 to 1.1% of the total volume of veterinary antimicrobial sales. Sales volume of human antimicrobials in companion animals was not originally monitored under JVARM and is therefore excluded from the values in the table for 2015 and earlier. Accordingly, with the full cooperation of the Japan Animal Agents & Instruments Dealers Association and Federation of Japan Pharmaceutical Wholesalers Association, the Ministry of Agriculture, Forestry and Fisheries began monitoring the actual usage of human antimicrobials in 2016. The results of its surveillance revealed that the volume of human antimicrobials sold for use in companion animals is slightly less than the volume of veterinary antimicrobials sold for that purpose. Including those for human antimicrobials, the most commonly sold antimicrobials were first-generation cephalosporins and penicillins.

Table 84. The estimated volumes of sales of veterinary and human antimicrobials for companion animals (dogs and cats) in terms of active ingredients (t)

	2013	2014	2015	2016		2017		2018		2019		2020	
	Animal	Animal	Animal	Animal	Human	Animal	Human	Animal	Human	Animal	Human	Animal	Human
Penicillins	2.36	2.13	2.08	1.57	1.93	1.68	1.75	1.66	2.14	1.64	1.98	1.54	1.56
Cephalosporins(total)	2.45	2.44	2.67	3.12	3.23	3.21	2.39	3.16	1.98	3.91	2.04	3.93	1.62
1st generation cephalosporins	(2.26)	(2.23)	(2.46)	(2.89)	(3.08)	(2.99)	(2.27)	(2.93)	(1.86)	(3.69)	(1.90)	(3.72)	(1.49)
2nd generation cephalosporins	(0.00)	(0.00)	(0.00)	(0.00)	(0.04)	(0.00)	(0.03)	(0.00)	(0.03)	(0.00)	(0.03)	(0.00)	(0.03)
3rd generation cephalosporins	(0.20)	(0.20)	(0.21)	(0.23)	(0.11)	(0.22)	(0.09)	(0.22)	(0.09)	(0.22)	(0.11)	(0.21)	(0.10)
Aminoglycosides	2.07	1.97	1.40	0.41	0.02	0.39	0.01	0.91	0.01	0.40	0.02	0.37	0.02
Macrolides	0.00	0.00	0.00	0.00	0.17	0.00	0.16	0.02	0.17	0.02	0.18	0.00	0.18
Lincosamides	0.09	0.09	0.11	0.13	0.10	0.13	0.10	0.14	0.10	0.15	0.09	0.15	0.08
Tetracyclines	0.00	0.00	0.00	0.00	0.28	0.00	0.31	1.27	0.33	0.53	0.35	0.42	0.34
Peptides	0.01	0.01	0.01	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00
Other antibioitics**	0.00	0.00	0.00	0.00	0.22	0.00	0.21	0.00	0.22	0.00	0.22	0.00	0.23
Sulfonamides	0.60	0.55	0.56	0.53	0.19	0.57	0.19	0.53	0.22	0.50	0.25	0.78	0.25
Quinolones	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Fluoroquinolones	0.90	0.90	0.94	0.89	0.11	0.90	0.11	0.84	0.12	0.87	0.16	0.88	0.11
Amphenicols	0.00	0.00	0.00	0.00	0.12	0.01	0.10	0.01	0.11	0.01	0.12	0.01	0.11
Furan and derivatives	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other synthetic antibacterials***.	0.02	0.01	0.01	0.01	0.08	0.01	0.10	0.01	0.10	0.00	0.13	0.02	0.11
Total	8.49	8.10	7.78	6.67	6.48	6.90	5.43	8.56	5.51	8.03	5.53	8.11	4.60

The figures in parentheses are included in the Cephalosporins (total).

** Includes fosfomycin and rifamycin, etc. (vancomycin for human was 0.0006t in 2016, 0.0005t in 2017, 0.0006t in 2018, 0.0006t in 2020)

*** Includes trimethoprim, penems, carbapenems, etc. (carbapenems for human was 0.0066t in 2016, 0.0057t in 2017, 0.0062t in 2018, 0.0083t in 2020)

(3) Antimicrobial feed additives

Source: Food and Agricultural Materials Inspection Center (FAMIC) and Japan Scientific Feeds Association

The volumes of distribution of antimicrobial feed additives, based on surveys by the Food and Agricultural Materials Inspection Center and by the Japan Scientific Feeds Association, are indicated in Table 84. While the volume of such additives distributed remained almost unchanged in the period 2013 to 2020, ranging between 235.1 t and 234.9 t, comparisons among the different types of antimicrobials showed an upward trend in the distribution of polyethers (not used in humans), which account for the majority. The designation of the polypeptide colistin as a feed additive was revoked in July 2018, followed by the macrolide tylosin in May 2019 and two tetracyclines in December 2019. Distribution of these antimicrobials ceased from the time their designation was revoked.

Table 85. Volume of distribution of antibiotic feed additives in terms of effective value (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Aminoglycosides	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Polypeptides	35.0	28.3	29.6	32.1	15.2	9.4	6.4	7.1
Tetracyclines	1.6	2.2	2.6	2.0	0.0	0.0	0.0	0.0
Macrolides	5.6	5.3	5.5	1.4	3.5	0.0	0.0	0.0
Polysaccharides	0.2	0.0	0.1	0.1	0.1	0.0	2.3	3.4
Polyethers	136.0	142.5	141.7	159.9	165.5	161.0	174.1	192.5
Other antimicrobials	20.8	18.3	12.5	14.6	19.8	26.2	17.6	11.9
Synthetic antimicrobials	35.9	29.3	24.4	18.1	17.1	20.1	25.1	20.0
Total	235.1	225.9	216.4	228.2	221.2	216.7	225.5	234.9

Figures do not include antifungal agents.

(4) Agrochemicals

Source: Plant Products Safety Division, Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries

The volume of shipment in Japan of antimicrobials that are used as agrochemicals is shown in the Table 86, in terms of active ingredients (unit: tons). In the period from 2013 to 2020, the volume of shipments of antimicrobials used as agrochemicals remained at around the 150 t mark, ranging from 135.90 to 181.43 t.

Table 86. The volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Streptomycin	45.19	45.30	44.41	49.80	56.04	36.19	35.90	37.52
Oxytetracycline	19.49	22.23	23.25	19.46	17.81	0.13	0.16	0.35
Kasugamycin	23.43	23.92	23.69	23.68	23.90	21.22	19.79	18.41
Validamycin	23.11	25.50	24.97	24.80	24.71	23.35	23.85	24.78
Oxolinic acid	40.08	40.79	41.16	42.17	44.38	44.53	43.29	41.33
Polyoxins	16.24	15.49	15.25	15.80	14.59	13.65	13.23	13.52
Total	167.54	173.24	172.73	175.71	181.43	139.07	136.22	135.90

Figures shown are for the agrochemical year (the 2013 agrochemical year ran from October 2012 to September 2013). Figures do not include antifungal agents.

(5) Current status of antimicrobial use in Japan

Table 88 shows the total use (or sales) of antimicrobials in humans, food producing animals, aquatic animals, companion animals, antimicrobial feed additives, and agrochemicals. Antimicrobial selection pressure in Japan from a One Health perspective has increased only 1.04 times even compared to 2013 and is highest among tetracyclines at 18-21%, followed by penicillins at 13-17%, and macrolides at 11-15%. Use of penicillins, and macrolides has been growing over recent years, so caution regarding future trends will be required. On the other hand, the fact that barely any changes in cephalosporins and fluoroquinolones were observed is attributed to differences in the antimicrobials that can be used in humans and in non-humans.

Table 87. Current volume of antimicrobial use (or sales) in Japan (t)

	2013	2014	2015	2016	2017	2018	2019	2020
Penicillins	222.0	229.1	249.2	262.8	268.5	279.9	302.8	265.5
Cephalosporins	168.2	163.7	166.5	165.3	160.4	156.7	154.9	131.2
Monobactams	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbapenems	9.9	9.9	10.1	10.2	10.1	9.8	10.0	8.8
Aminoglycosides	97.2	98.8	93.1	109.1	104.1	93.7	91.6	93.3
Macrolides	191.3	177.1	207.4	238.4	238.9	244.4	267.9	241.5
Lincosamides	41.8	46.0	31.3	24.3	27.6	25.1	24.1	23.6
Tetracyclines	359.7	345.9	356.0	351.3	363.7	318.7	320.9	313.1
Peptides and glycopeptides	49.0	40.4	46.4	48.5	37.7	24.1	28.6	28.7
Sulfonamides*.	149.7	147.5	150.4	154.4	161.2	154.4	155.7	174.3
Fluoroquinolones	66.8	65.8	63.9	63.5	60.0	56.7	55.3	40.1
Other quinolones	41.6	43.1	43.2	44.3	46.0	46.1	46.0	43.8
Amphenicols, thiamphenicols and derivatives	21.8	26.2	29.8	26.6	27.2	24.9	27.5	25.6
Furan and derivatives	14.5	1.8	1.2	1.6	1.4	1.3	1.4	1.2
Polysaccharides	0.2	0.0	0.1	0.1	0.1	0.0	2.3	3.4
Polyethers	136.0	142.5	141.7	159.9	165.5	161.0	174.1	192.5
Polyoxins	16.2	15.5	15.3	15.8	8.6	13.7	13.2	13.5
Others*.	138.4	132.6	124.6	118.6	122.8	133.3	127.4	115.2
Total	1724.3	1685.9	1730.2	1795.0	1803.7	1743.9	1803.4	1715.5

*Sulfonamides used as antimicrobial feed additives and the agrochemical validamycin are included in “Others.” Figures do not include antifungal agents.

Table 88. Changes in the volume of antimicrobial use (or sales) in Japan by year (unit: metric tons) (cont.)

	2013						2014						2015					
	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals
Penicillins	143.8	59.5	16.3	2.4	0.0	0.0	151.1	62.0	13.9	2.1	0.0	0.0	165.4	67.3	14.4	2.1	0.0	0.0
Cephalosporins	162.6	3.1	0.0	2.5	0.0	0.0	158.2	3.1	0.0	2.4	0.0	0.0	160.6	3.2	0.0	2.7	0.0	0.0
Monobactams	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
Carbapenems	9.9	0.0	0.0	0.0	0.0	0.0	9.9	0.0	0.0	0.0	0.0	0.0	10.1	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	1.0	37.4	0.0	2.1	0.0	56.7	0.9	38.7	0.0	2.0	0.0	57.2	0.9	34.1	0.0	1.4	0.0	56.7
Macrolides	108.0	56.0	21.7	0.0	5.6	0.0	101.4	53.3	17.1	0.0	5.3	0.0	103.4	60.4	38.1	0.0	5.5	0.0
Lincosamides	2.8	35.9	3.0	0.1	0.0	0.0	2.7	36.6	6.6	0.1	0.0	0.0	2.6	23.7	4.9	0.1	0.0	0.0
Tetracyclines	7.1	286.7	53.8	0.0	1.6	10.5	6.9	275.8	49.0	0.0	2.2	12.0	7.1	276.2	57.6	0.0	2.6	12.5
Peptides and glycopeptides	2.2	11.8	0.0	0.0	35.0	0.0	2.1	10.0	0.0	0.0	28.3	0.0	2.3	14.5	0.0	0.0	29.6	0.0
Sulfonamides	45.8	95.6	7.7	0.6	0.0	0.0	49.9	88.4	8.6	0.6	0.0	0.0	53.7	84.4	11.7	0.6	0.0	0.0
Fluoroquinolones	61.3	4.6	0.0	0.9	0.0	0.0	60.2	4.7	0.0	0.9	0.0	0.0	56.6	6.4	0.0	0.9	0.0	0.0
Other quinolones	0.5	0.2	0.8	0.0	0.0	40.1	0.4	0.2	1.7	0.0	0.0	40.8	0.3	0.2	1.5	0.0	0.0	41.2
Amphenicols, thiamphenicols and derivatives	0.2	19.7	1.9	0.0	0.0	0.0	0.1	25.1	1.0	0.0	0.0	0.0	0.1	27.4	2.3	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	14.5	0.0	0.0	0.0	0.0	0.0	1.8	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
Polyethers	0.0	0.0	0.0	0.0	136.0	0.0	0.0	0.0	0.0	0.0	142.5	0.0	0.0	0.0	0.0	0.0	141.7	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	16.2	0.0	0.0	0.0	0.0	0.0	15.5	0.0	0.0	0.0	0.0	0.0	15.3
Others*	17.6	40.7	0.3	0.0	56.7	23.1	16.6	42.4	0.5	0.0	47.6	25.5	16.9	45.6	0.2	0.0	36.9	25.0
Total	563.0	651.2	119.9	8.5	235.1	146.6	560.6	640.2	100.1	8.1	225.9	151.0	580.1	643.3	131.9	7.8	216.4	150.7
Total for year						1,724.3						1,685.9						1,730.2

Table 88. Changes in the volume of antimicrobial use (or sales) in Japan by year (unit: metric tons) (cont.)

	2016						2017						2018					
	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals
Penicillins	172.7	73.8	14.6	1.6	0.0	0.0	180.3	71.7	14.7	1.7	0.0	0.0	190.8	74.5	12.9	1.7	0.0	0.0
Cephalosporins	158.9	3.3	0.0	3.1	0.0	0.0	153.8	3.4	0.0	3.2	0.0	0.0	149.6	3.9	0.0	3.2	0.0	0.0
Monobactams	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
Carbapenems	10.2	0.0	0.0	0.0	0.0	0.0	10.1	0.0	0.0	0.0	0.0	0.0	9.8	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	0.8	47.5	0.0	0.4	0.0	60.4	0.8	44.4	0.0	0.4	0.0	58.5	0.7	34.7	0.0	0.9	0.0	57.4
Macrolides	102.9	72.7	61.4	0.0	1.4	0.0	94.5	72.0	68.9	0.0	3.5	0.0	89.7	72.1	82.6	0.0	0.0	0.0
Lincosamides	2.5	15.6	6.1	0.1	0.0	0.0	2.4	19.4	5.7	0.1	0.0	0.0	2.4	16.7	5.9	0.1	0.0	0.0
Tetracyclines	7.2	280.7	50.9	0.0	2.0	10.5	7.0	286.0	61.1	0.0	0.0	9.6	7.3	257.4	52.6	1.3	0.0	0.1
Peptides and glycopeptides	2.4	14.0	0.0	0.0	32.1	0.0	2.5	20.0	0.0	0.0	15.2	0.0	2.4	12.3	0.0	0.0	9.4	0.0
Sulfonamides	58.6	78.6	16.7	0.5	0.0	0.0	62.1	84.1	14.4	0.6	0.0	0.0	65.7	78.6	9.6	0.5	0.0	0.0
Fluoroquinolones	57.4	5.2	0.0	0.9	0.0	0.0	53.2	5.9	0.0	0.9	0.0	0.0	50.1	5.8	0.0	0.8	0.0	0.0
Other quinolones	0.3	0.2	1.6	0.0	0.0	42.2	0.2	0.3	1.5	0.0	0.0	44.0	0.1	0.0	1.5	0.0	0.0	44.5
Amphenicols, thiamphenicols and derivatives	0.1	24.8	1.7	0.0	0.0	0.0	0.1	25.3	1.8	0.0	0.0	0.0	0.1	23.3	1.5	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Polyethers	0.0	0.0	0.0	0.0	159.9	0.0	0.0	0.0	0.0	0.0	165.5	0.0	0.0	0.0	0.0	0.0	161.0	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	15.8	0.0	0.0	0.0	0.0	0.0	8.6	0.0	0.0	0.0	0.0	0.0	13.7
Others*	17.0	43.6	0.5	0.0	32.7	24.8	14.6	48.7	0.5	0.0	36.9	22.1	14.1	48.8	0.7	0.0	46.3	23.4
Total	591.4	659.9	155.1	6.7	228.2	153.6	581.6	681.3	169.9	6.9	221.2	142.7	582.9	628.1	168.5	8.6	216.7	139.1
Total for year						1795.0						1803.7						1743.9

Table 88. Changes in the volume of antimicrobial use (or sales) in Japan by year (unit: metric tons) (cont.)

	2019						2020					
	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals
Penicillins	210.4	73.8	17.0	1.6	0.0	0.0	168.6	76.2	19.2	1.5	0.0	0.0
Cephalosporins	146.9	4.1	0.0	3.9	0.0	0.0	123.5	3.8	0.0	3.9	0.0	0.0
Monobactams	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
Carbapenems	10.0	0.0	0.0	0.0	0.0	0.0	8.8	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	0.7	34.8	0.0	0.4	0.0	55.7	0.5	36.5	0.0	0.4	0.0	55.9
Macrolides	87.2	73.3	107.4	0.0	0.0	0.0	67.8	72.7	101.0	0.0	0.0	0.0
Lincosamides	2.7	16.3	4.9	0.2	0.0	0.0	2.1	17.5	3.8	0.2	0.0	0.0
Tetracyclines	7.7	242.9	69.6	0.5	0.0	0.2	8.4	240.1	63.8	0.4	0.0	0.4
Peptides and glycopeptides	2.6	19.6	0.0	0.0	6.4	0.0	2.7	19.0	0.0	0.0	7.0	0.0
Sulfonamides	71.0	68.6	15.6	0.5	0.0	0.0	75.7	84.4	13.4	0.8	0.0	0.0
Fluoroquinolones	47.7	6.7	0.0	0.9	0.0	0.0	33.0	6.2	0.0	0.9	0.0	0.0
Other quinolones	0.1	0.1	2.5	0.0	0.0	43.3	0.1	0.2	2.2	0.0	0.0	41.3
Amphenicols, thiamphenicols and derivatives	0.1	23.9	3.5	0.0	0.0	0.0	0.1	23.1	2.4	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	1.4	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	3.4	0.0
Polyethers	0.0	0.0	0.0	0.0	174.1	0.0	0.0	0.0	0.0	0.0	192.5	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	13.2	0.0	0.0	0.0	0.0	0.0	13.5
Others*	13.4	47.3	0.3	0.0	42.7	23.8	10.5	47.1	0.9	0.0	31.9	24.8
Total	600.2	611.4	222.1	8.0	225.5	136.2	501.9	626.8	208.0	8.1	234.8	135.9
Total for year						1,803.4						1715.5

*Sulfonamides used as antimicrobial feed additives and the agrochemical validamycin are included in "Others." Antifungal antibiotics used as veterinary agents are not included in "Others." Figures do not include antifungal agents.

(6) Research into antimicrobial stewardship

The following provides a summary of past reports on studies related to the appropriate use of antimicrobial agents in Japan and those published since this report last year (from the latter half of 2020). It covers only studies using medical insurance claims data for outpatient consultations across the whole of Japan and excludes studies limited to a specific region and studies that analyzed only the amount of antimicrobials used. The medical insurance claims data used includes the NDB[2,3] developed by the Ministry of Health, Labour and Welfare, the National Health Insurance database,[4] and commercial databases created by combining medical insurance claims data from multiple health insurance societies (JMDC Inc.'s JMDC Claims Database[1, 5-7], IQVIA Inc.'s IQVIA Claims8, and MDV's MDV analyzer[11]). Unless otherwise indicated, figures in square brackets ([]) in the text show the 95% confidence interval.

1. Past reports on antimicrobial stewardship

Studies have been reported on the appropriate use of antimicrobial agents for acute respiratory tract infections and acute diarrhea, which are addressed in the Manual of Antimicrobial Stewardship[1-7]. It was suggested that although antimicrobial use has been gradually decreasing, there is still room for intervention to support appropriate use, as there are still many prescribed for acute respiratory tract infections and acute diarrhea. In this context, in 2018, the appropriate use of pediatric antimicrobial agents was introduced as a premium national health insurance (NHI) item for children under 3 years of age, and the eligible age was further raised to under 6 years of age in the 2020 revision. Muraki et al. examined the effect of this premium item in 2018 for children under 15 years of age using the IQVIA's database, revealing that the percentage of antimicrobial prescriptions was lower at facilities that had claimed this premium item compared to those that had not.[8] In addition to these results, the eligible age range for the item is being expanded, and expansion of the study period and age, and more detailed investigation of the effect on appropriate use of antimicrobials with and without age-specific introduction are also to be considered for the promotion of appropriate use of antimicrobial agents in the future. As for children, a new study investigating the effects of action plans targeting pediatric clinics has been reported and is described in the next section.[9] With regard to acute diarrhea, Okubo et al. previously showed antimicrobial use from April 2012 to December 2015 for children (<18 years old) using the JMDC's database7. Insurance claims on 4,493 outpatients with acute diarrhea were studied, of which 29.6% of the patients were prescribed some type of antimicrobial agent, with fosfomycin being the most common antimicrobial agent (20.3%). For adults, Ohno et al. used the JMDC database to investigate antimicrobial use for acute diarrhoea among 0–65-year-olds from January 2013 to December 2018.[10] Over the 6-year study period, 94.6% of all subjects had non-bacterial diarrhoea, but the antimicrobial prescription rate (number of prescriptions/visits) was 46.5% in adult males and 40.8% in adult females. The antimicrobial prescription rate for children (0-17 years) was 30.5% for boys and 30.4% for girls, which was not significantly different from a previous survey by Okubo et al. [7] Sugiyama et al. also investigated the status of oral antimicrobial prescriptions for acute diarrhoea using a practice database-based analysis tool (MDV analyzer: Medical Data Vision Inc., Tokyo, Japan). [11] The investigation was conducted between January 2013 and December 2019 with hospitals participating in the Diagnosis Procedure Combination / Per-Diem Payment System and registered on the MDV analyzer nationwide, which showed that the number of patients prescribed has decreased over time, similarly to the results of Ohno et al.'s study.

2. New research reports on the antimicrobial stewardship

[Study on the impact of the introduction of the premium for appropriate use of pediatric antimicrobials].

Using the JMDC database, Jindai et al. investigated the impact of the premium, introduced in April 2018, that offers incentives for not prescribing antimicrobials for respiratory tract infections and diarrhoea (0-2 years) and the healthcare provider education (6 years and older) based on the information from April 2013 to February 2020. The effect was assessed using interrupted time series analysis.[12] The results showed that antimicrobial prescribing decreased significantly after the introduction of the premium in the 0-2 age group (-47.5 prescriptions [77.3 to -17.6] per 1,000 monthly clinic visits). Education for healthcare providers reduced antimicrobial prescribing for all ages. These showed an immediate effect after introduction, but no long-term effect.

Okubo et al. used NDB to similarly assess the effect of the premium using a difference-in-differences analysis and found a reduction in antimicrobial prescribing (DID estimate, -228.6 DOT per 1,000 cases [95% confidence interval -272.4 to -184.9]).[13]There was also no increase in out-of-hour consultations with treatment of respiratory symptoms (DID estimate, -256.9 DOT [-379.3 to -134.5] per 1,000 cases) or antihistamines (DID estimate, -198.5 DOT [-282.1 to -114.9] per 1,000 cases) [DID estimate, -4.43 per 1,000 cases [-12.8 to -3.97]. There was also no increase in hospital admissions [DID estimate, -0.08 per 1,000 cases [-0.48 to 0.31]. The study showed that it led to a reduction in unnecessary antimicrobial prescribing without any negative impact on healthcare.

[Research on prescribing status]

Using JMDC, Sato et al. analyzed the prescribing of prophylactic antimicrobials after tooth extractions for people aged 18 years and older between September 2015 and August 2018 to investigate the impact of the AMR

action plan.[14] The results showed that of the 662, 435 eligible patients, those who were prescribed prophylactic antimicrobials accounted for 83% of the overall patients and 82% of those defined as being at low risk of post-operative infection. Although this proportion did not change within the study period, the breakdown by class showed a decrease in the prescriptions for third-generation cephalosporins from 58% to 34% (hospitals) and from 57% to 56% (clinics).

There was an increase in amoxicillin from 16% to 37% (hospitals) and from 6% to 10% (clinics).

Araki et al. also used JMDC to survey 18,659 working-age population members who had undergone medical examinations for at least five years and had been diagnosed with the common cold at least twice between January 2005 and February 2016. [15] The results showed that 49.2% (9,180 patients) were prescribed antimicrobials, and it was revealed that its factors included lack of chronic disease, male patients, and clinics or hospitals with less than 20 beds. In addition, 40-45% were prescribed cephalosporins. In interpretation, it should be noted that the study subjects were from the working-age population.

The situation of inappropriate prescribing was revealed, with cephalosporins being the most commonly used, indicating the need to promote ASP.

3. New data collection and analysis methods for appropriate use of antimicrobial agents

A system is being developed to tabulate the percentage of antimicrobial use for respiratory tract infections using NDB information. We are examining the ratio of antimicrobial prescriptions for specific illnesses and injuries. Monitoring by region, age group, and type of antimicrobial agent is planned.

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(7) Environment

Pharmaceutical products including antimicrobials, agents and daily necessities, are collectively referred to as "Pharmaceuticals and Personal Care Products (PPCPs)." PPCPs may have physiological activity even at low concentration, causing concerns about effect on aquatic ecosystems.[10] Regarding antimicrobials as a type of PPCPs, several studies have indicated the measurements of antimicrobial concentrations in the environment (e.g. sewage, treated wastewater, recycled water, environmental water, and sludge).[11]

In some cases, a part of sewage sludge (biomass) that is generated from sewage treatment is reused as agricultural fertilizers through anaerobic digestion and composting. The extent to which PPCPs are degraded in the sewage treatment process or in the sewage sludge digestion process varies by the type of PPCPs. For example, among other antimicrobials, most sulfonamides are decomposed, while fluoroquinolones, such as ofloxacin and norfloxacin, reside in sludge at high concentrations without being degraded.[12] The biodegradation process of PPCPs is affected by water temperature. The removability of PPCPs is affected by treatment conditions in the sewage treatment process, such as hydraulic retention time, the processing concentration and retention time of activated sludge. To further promote removal, research is in progress to improve the removability of antimicrobials using membrane bioreactor.[10] Many research activities are also undertaken both in Japan and overseas to improve efficiency in removing antimicrobials, by introducing ozone and advanced oxidation process. It is required to identify the current status of discharge and developmental trends in Japan.[11]

A study that measured the concentrations of antimicrobials detected in Japanese urban rivers, based on influent sewage at sewage treatment plants, reported that the actual measurements of CPFX and clarithromycin indicated certain similarity to concentrations expected from the volumes of shipment or sales of these antimicrobials, and pointed out that it may be possible to predict sewage concentrations of antimicrobials based on their volumes of shipment or sales.[13] The study reported that, for example, CPFX and clarithromycin were contained in sewage at the respective concentrations of 51 to 442 ng/L and 886 to 1,866 ng/L. In addition, in the environmental survey of chemical substances conducted by the Ministry of the Environment, a maximum of 130 ng/L of azithromycin, 2.3 ng/L of amoxicillin, 3.1 ng/L of thiamulin, 540 ng/L of levofloxacin, and 240 ng/L of clarithromycin were detected and up to 1.4 ng/L of ampicillin have been detected in river water and other water.[14, 15, 16]

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8. Public Awareness regarding Antimicrobial Resistance in Japan

(1) Surveys of the general public

1) Surveys of attitudes among the public

Ohmagari et al. conducted surveys of public awareness concerning antimicrobial resistance in March 2017, February 2018, September 2019, and September 2020 funded by a Ministry of Health, Labour and Welfare research grant.[1, 2, 3] In these studies, consumers (excluding medical professionals) who had registered with INTAGE Research Inc. to participate in various market research surveys completed an online questionnaire. The 2017 survey had 3,390 respondents, the 2018 survey 3,192, the 2019 survey 3,218, and the 2020 survey 3,200. Women comprised 48.8% of respondents in 2017, 49.7% in 2018, 52.2% in 2019, and 50.4% in 2020. Until 2019, more than 40% of all respondents experienced taking antibiotics because of cold, which decreased to 29.8% in 2020. Similarly, approximately 40% of respondents thought that antibiotics were effective for cold and influenza. Approximately 20% discontinued taking antibiotics based on their own judgment; and approximately 10% kept the remaining antibiotics at home. Among the respondents who kept antibiotics at home, approximately 80% used them based on their own judgment. The trends in responses to each survey were more or less the same, so ongoing efforts to raise public awareness using a variety of measures are required in order to change attitudes among the public.

Table 89. Reasons for taking oral antibiotics (%)

n=3,390 (2017), 3,192 (2018), 3,218 (2019), 3,200 (2020) (select all that applied)	2017 (%)	2018 (%)	2019 (%)	2020 (%)
Cold	45.5	44.7	41.2	29.8
Others/unknown	24.3	21.2	23.2	30.4
Influenza	11.6	12.4	12.0	5.8
Fever	10.7	11.3	8.5	7.8
Nasopharyngitis	9.5	10.8	10.5	9.9
Cough	9.0	10.8	6.9	4.5
Sore throat	7.7	7.8	8.2	7.1
Skin or wound infection	6.5	7.0	9.0	14.5
Bronchitis	5.4	6.6	5.1	5.9
Headache	4.3	5.0	4.1	5.0
Diarrhea	3.1	3.2	2.6	3.1
Urinary tract infection	2.3	2.5	2.7	4.7
Pneumonia	1.4	1.7	1.3	1.2

Table 90. Do you think each of the following statements is correct or incorrect? (%)

		2017 (n=3,390)	2018 (n=3,192)	2019 (n=3,218)	2020 (n=3,200)
Antibiotics beat viruses	Correct	46.8	46.6	52.4	42.6
	Incorrect	21.9	20.3	17.7	23.5
	Do not know	31.3	33.0	29.9	33.9
Antibiotics have effect on cold and influenza	Correct	40.6	43.8	43.9	40.4
	Incorrect	24.6	22.1	22.7	23.1
	Do not know	34.8	34.1	33.4	36.4
Unnecessary use of antibiotics may result in the loss of their effect	Correct	67.5	68.8	66.4	64.9
	Incorrect	3.1	3.7	3.4	3.3
	Do not know	29.4	27.5	30.2	31.8
Adverse effects are involved in the use of antibiotics	Correct	38.8	41.5	45.7	45.6
	Incorrect	12.7	13.4	10.5	9.9
	Do not know	48.6	45.0	43.8	44.5

Table 91. Do any of the statements below apply to you? (%)

		2017 (n=3,390)	2018 (n=3,192)	2019 (n=3,218)	2020 (n=3,200)
I have discontinued taking antibiotics, or adjusted a dose or frequency based on my own judgment	Yes	23.6	24.0	24.6	23.3
	No	76.4	76.0	75.4	76.7
I keep antibiotics in my house	Yes	11.7	11.9	9.8	9.3
	No	88.3	88.1	90.2	90.7

Table 92. Do any of the statements below apply to you? (%)

		2017 (n=396*)	2018 (n=426*)	2019 (n=3,218)	2020 (n=298)
I have used antibiotics that I kept at home for myself	Yes	75.8	77.5	75.6	76.2
	No	24.2	22.5	24.4	23.8
I have given antibiotics that I kept at home to my family or friend	Yes	26.5	27.2	28.5	25.5
	No	73.5	72.8	71.5	74.5

* Only respondents with valid responses that kept antibiotics at home.

2) Surveys of perception of antimicrobial agents and treatment-seeking behavior among 20-30-year-olds

Surveillance based on the National Database for Prescription and National Health Checkups (NDB) shows that the use of antimicrobial agents (DID) is higher among women than among men in all age groups, especially among women aged 20-39. To find out the reason for this, an Internet survey was conducted in February 2021 on how antimicrobial agents are perceived and how they seek treatment, targeting 1,000 respondents each for males, females, aged 20-29, and aged 30-39, for a total of 4,000 respondents. 22.6% of men and 36.1% of women reported having visited a hospital or clinic (including dentistry) at least 6 times during the past year, with women having more frequent visits. 38.6% of men and 38.4% of women reported that antimicrobial agents were prescribed during their visits. 40.2% of men and 24.3% of women reported that the reason they were prescribed antimicrobials was a cold. 22.2% of men and 18.3% of women had requested for antimicrobial agents at a hospital or clinic. 11.6% of men and 8.4% of women went to see a doctor immediately when they caught a cold, and 31.2% of men and 39.8% of women thought it was better to take medicine instead of trying to be stoic when feeling sick. The survey results showed no difference between men and women in the percentage of those who are prescribed antimicrobial agents per visit, suggesting that the difference in the number of visits is the cause of the difference in the use of antimicrobial agents between men and women. In order to effectively promote the proper use of antimicrobial agents, it is necessary to consider specific messages that also take into account awareness and attitudes toward infectious diseases and antimicrobial agents, as well as treatment-seeking behavior.

(2) Surveys of healthcare providers

1) Awareness survey of clinic physicians

The Joint Survey Committee on Appropriate Use of Antimicrobial Agents in Outpatients of the Japanese Society of Chemotherapy and the Japanese Association of Infectious Diseases conducted the second survey of awareness among physicians working in clinics in February 2018 and from September to October 2020. The survey questionnaire was distributed to 3,000 randomly selected clinics nationwide, and the forms were filled and returned. Compared to the survey in 2018, awareness of the Action Plan increased, and the number of respondents who answered that they had "never heard of it" decreased from 44.9% to 34.8% (Table 93). The percentage of antimicrobial prescriptions for common cold decreased from 62.0% to 71.1% with "0-20%" as the percentage of prescriptions (Table 95). Responding to requests for antimicrobial prescriptions, 35.5% of the respondents said they would "explain and not prescribe," while 10.8% and 49.1% said they would "prescribe as requested" and "prescribe if not satisfied after explanation," respectively, hardly different from the results of the previous survey (Table 96). It is possible that intention to be actively involved in patient education and communication is not necessarily high. 44.7% "never," 28.7% "not very often," 24.1% "sometimes," and 2.5% "always" take antimicrobial agents when they themselves have a common cold, and 39.1% "never," 31.5% "not very often," and 27.4% "sometimes," and 2.1% "always" recommend antimicrobial agents when their family member has a common cold. These results suggest that physicians who prescribe more antimicrobial agents for common cold may be expecting a therapeutic effect when prescribing them. As in the previous survey, the percentage of prescribing antimicrobial agents for acute bronchitis was also high (Table 97).

(Fig. 1). The development of simpler pathogen diagnostic tests may be effective in promoting the appropriate use of antimicrobial agents. Doctors aged 60 years or older were more aware of the appropriate use of antimicrobial agents than physicians younger than 60 years (69.6% vs. 58.5%). However, the percentage of respondents who prescribed antimicrobial agents to "20% or less" of those diagnosed with common cold was less than those under 60 (79.5% vs. 65.3%), suggesting that although they understood the importance of agent resistance control, this did not necessarily lead to prescribing behaviour (Tables 97 and 98). The majority of respondents cited campaign to the public as necessary to achieve the action plan, which was unchanged from the previous survey.

Table 93

Awareness of Action Plan (%)	2018 (n=267)	2020 (n=627)
I can explain it to people.	1.9	3.5
I understand it.	21.0	27.8
I only know the name.	32.2	33.1
I have no idea.	44.9	34.8

Table 94

Percentage of antimicrobial agents prescribed when diagnosing a common cold (%)	2018 (n=242)	2020 (n=543)
0-20%	62.0	71.1
21-40%	17.8	16.6
41-60%	7.4	6.8
61-80%	8.3	3.5
81% or more	4.5	2.0

Table 95

Response when patients or family members diagnosed with common cold request for antimicrobial agent (%)	2018 (n=252)	2020 (n=609)
Prescribe it if they are not convinced by explanation	50.4	49.1
Explain and not prescribe	32.9	35.5
Prescribe as requested	12.7	10.8
Other	3.7	4.6

Table 96

Frequency of antimicrobial prescription when diagnosing an acute bronchitis was diagnosed (in the past year) (%)	2018 (n=232)	2020 (n=522)
0-20%	31.0	35.4
21-40%	23.7	24.9
41-60%	14.2	15.7
61-80%	9.5	9.0
81% or more	21.6	14.9

Table 97

How much aware of the appropriate use of antimicrobial agents in the past year (%)	Always/quite aware	Somewhat/not at all consciously
Under 60 years old	58.5	41.5
60 years old and over	69.6	30.4

Table 98

Frequency of antimicrobial prescription when diagnosing a common cold (in the past year) (%)	20% or less	20% or more
Under 60 years old	79.5	20.5
60 years old and over	65.3	34.7

2）Research on infectious diseases and antimicrobials in pharmacy education

Pharmacists are important members of the healthcare team responsible for in-hospital and community ICT and ASP activities, and the need for education on AMR and clinical infectious diseases among pharmacists is increasing. However, the current state of education on clinical infectious diseases in the faculty of pharmacy of Japanese universities was not clear, so a nationwide survey of pharmacy schools in Japan was conducted from February to March 2022. Questionnaires were sent to pharmacy schools across Japan, and 44 out of 74 universities responded.

The median number of teaching staff members in charge of infectious disease education was 7 [4-12], of which practitioners were 3 [1-6].

62.8% of the universities had teaching staff members with clinical experience in infectious diseases. Regarding the contents of education, the most frequently reported as “inadequate” or “not implemented” were: the concept of prophylactic antimicrobials in the perioperative period (74.5% inadequate or not implemented in total), how to explain to patients when antimicrobial is not necessary (76.8% in total), patient education on prudent antimicrobial use (79% in total), team approach to infectious disease care and infection control (53.5% in total), and education on antimicrobial research and development (76.8% in total). Insufficient time for lectures and lack of specialists were the top issues in clinical infectious disease education. The survey also revealed that educational status and resources for clinical infectious diseases and AMR varied widely. It was suggested that resources, including the overall curriculum and the number of teachers, need to be examined and improved.

(3) Survey of veterinary medicine students

The Ministry of Agriculture, Forestry and Fisheries conducted an awareness survey among veterinary students nationwide. The survey was conducted in the form of a questionnaire via the internet between April 2021 and March 2022, and 404 students from eight universities (183 third-grade students, 108 fourth-grade students, and 113 fifth-grade students) responded.

Regarding the question about antimicrobials (Table 99), 10.4% of the students answered that they “work against influenza,” while 91.0% answered that they “work against bacterial infections". The number of students with correct knowledge tends to increase as they progress through university, which infers that students acquire a certain level of knowledge about antimicrobial agents in the course of veterinary medicine education.

As for what they know about drug resistance control in the veterinary field (Table 100), although a high percentage of students chose "Reducing opportunities for infections to occur through thorough implementation of biosecurity measures will contribute to drug resistance control." and “Partnership between the veterinary and human medicine fields,” they were less than a half. In addition, only 29.0-42.1% of the students were aware of the important knowledge for practicing agent resistance control, such as "reduction of infection opportunities leads to agent resistance control" through vaccination and feeding hygiene control and "second line agents". Furthermore, only about 20% of the students were aware of the initiatives taken by the public administration to combat drug resistance, such as the Antimicrobial Resistance Action Plan, drug resistance monitoring in the livestock sector, and the determination of risk management measures based on risk assessments.

Because veterinarians play a key role in agent resistance control in the veterinary field, it is important to continue to educate veterinary students on the correct knowledge and prudent use of antimicrobial agents.

Table 99. Please give your perceptions about antimicrobials (%)

	3rd year (n=183)	4th year (n=108)	5th year (n=113)	whole (n=404)
Effective against common cold	33.9	29.6	31.9	32.2
Effective against influenza infections	16.4	6.5	4.4	10.4
Effective against bacterial infections	90.7	89.8	92.9	91.0
Used to prevent complications after surgery	58.5	64.8	75.2	64.9
Used as a feed additive to be mixed with feed	45.9	33.3	42.4	41.6
Used in pesticides for vegetables and other produce	19.7	11.1	6.2	13.6

Table 100. Please select what you know about drug resistance control in the veterinary sector (%)

	3rd year student (n=183)	4th year student (n=108)	5th year (n=113)	whole (n=404)
An action plan on antimicrobial resistance (AMR) has been developed and is being implemented	16.9	15.7	24.8	18.8
The existence of antimicrobial agents called second-line agents	20.2	33.3	54.9	33.4
About Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)	17.0	21.3	18.6	18.6
Reduction of infection opportunities through vaccination contributes to drug resistance control.	32.8	20.4	31.0	29.0
Reduction of infection opportunities through thorough implementation of biosecurity measures contributed to drug resistance control.	38.9	43.5	46.0	42.1
Partnership between the veterinary and human medicine fields	39.9	50.9	46.0	44.6
Determination of risk management measures based on risk assessment	18.6	25.9	21.2	21.3
I don't know	24.0	15.7	10.6	18.1

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9. Way Forward

This document follows on from last year's report in presenting information on the current status of antimicrobial resistance in Japan in the areas of human health, animals, agriculture, food and the environment, as well as the volumes of use (or sales) of human and veterinary antimicrobials. Based on this current report, it is expected that AMR-related measures will be further advanced by promoting multi-disciplinary cooperation and collaboration. It is also considered crucial to continue with advanced surveillance activities, in order to take the leadership in global policy in AMR. Part of this report includes data obtained after Japan's "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020" was published. Following on from 2017, figures for 2018 show that the total usage of all antimicrobials and usage of oral antimicrobials, including oral cephalosporins, oral macrolides, and oral fluoroquinolones, is trending downward compared with the data for 2013. However, further promotion of measures against AMR will be required to achieve the 2020 targets. More specifically, it will be necessary to reduce the unnecessary prescription of antimicrobials, particularly in cases of acute respiratory tract infection, based on the Manual of Antimicrobial Stewardship, among other materials. As the basic premise underpinning the promotion of antimicrobial stewardship is ensuring that the appropriate antimicrobials can be used when needed, securing a stable supply of basic antimicrobial agents is crucial. In addition, it is desirable to select antimicrobials and promote appropriate infection control measures tailored to the situation in each region by using systems such as J-SIPHE and the Antimicrobial Resistance (AMR) One Health Platform to utilize information about resistant bacteria in each region and the status of antimicrobial use. Furthermore, it will be necessary to continue using various techniques for education and awareness activities targeting the public and medical professionals, to achieve further progress in antimicrobial stewardship.

In animal field, rates of resistance to third-generation cephalosporins and fluoroquinolones in *Escherichia coli* isolated from diseased companion animals, surveillance of which began in 2017, were found to be higher than in *Escherichia coli* isolated from food-producing animals. This demonstrates the necessity of continuing and enhancing measures to combat antimicrobial resistance not only via the measures that have been underway for some time in the field of food-producing animals, but also through the widespread circulation of the guide to prudent use in companion animals launched in 2020. In addition, the resistance rate of *E. coli* from healthy livestock animals to third generation cephalosporins and fluoroquinolones, which are the outcome indicators of the Action Plan, has remained low, and the target has been met.

In food-producing animal field, although the volume of tetracycline sales fell in 2018 and 2020, rates of tetracycline resistance in *Escherichia coli* isolated from healthy food-producing animals—an outcome index for the Action Plan—have not changed. Therefore, it is necessary to continuously reduce opportunities to use antimicrobials through the development, commercialization, and promotion of the use of vaccines and alternatives to antimicrobials and to promote appropriate and prudent use of antimicrobials, while monitoring trends in their resistance rates.

Following on from 2019, this report makes comparisons between the volume of antimicrobial use (or sales) in the fields of human medical care, veterinary care, and agriculture. Major progress was thus seen in such areas as the highlighting of differences in the volume of antimicrobial use in each field by type of antimicrobial, the reporting of antimicrobial resistance rates in healthy companion animals to accompany existing reporting on rates in diseased companion animals, and the enhancement of data on trends in antimicrobial-resistant bacteria in food and the environment. Hopes are high that progress in the surveillance of trends in each field will continue next year and beyond. Furthermore, it is hoped that initiatives of the kind spotlighted by the National Action Plan on Antimicrobial Resistance, focusing on linking data from antimicrobial resistance trend surveillance and monitoring in such areas as human health, animals, and food, will contribute to combating antimicrobial resistance in Japan in the future.

The existing Action Plan covers the five-year period up to 2020. Although some indices are improving, there are still many that have seen only scant improvement, added to which a number of new issues have emerged, so it is necessary to continue addressing them in coordination with international trends. As such, industry, academia, and government will work together to promote frameworks for collaboration between the organizations tasked with handling different fields, while also examining the promotion of research that enables cross-cutting evaluation of the risks to humans, animals, and the environment to be conducted.

Appendix

(1) Japan Nosocomial Infections Surveillance (JANIS)

1) Overview

JANIS is conducted for the purpose of having an overview of nosocomial infections in Japan, by surveying the status of health care associated infections at medical institutions in Japan, the isolation of antimicrobial-resistant bacteria, and the status of infections caused by antimicrobial-resistant bacteria, while providing useful information for the control of health care associated infections in medical settings. The aggregated data of information from all medical institutions patriated are published on the website of the National Institute of Infectious Diseases (https://janis.mhlw.go.jp/english/index.asp). A result of the analysis is reported back to each institution so that such a feedback can be utilized for the formulation and evaluation of infection control measures at each institution. JANIS participation is voluntary with approximately 2,000 participating medical institutions at present.

Clinical Laboratory Division of JANIS collects the laboratory data of bacteria that are isolated at hospitals across Japan, and publish aggregated data regarding the proportion of clinically important bacterial species that are resistant to major antimicrobials. In 2022, 2,340 hospitals participated in the laboratory section. The aggregated data include data from hospitals with at least 20 beds, and exclude clinics and facilities for the elderly. Since 2014, figures have also been compiled on the basis of hospital scale, divided into hospitals with 200 or more beds and those with fewer than 200 beds. Bacteria that are isolated from specimens from inpatients as well as outpatients at participating hospitals are included into aggregated data. To provide more representative information as a national surveillance system, protocols of sampling including selection of sentinel sites and their stratification need to be improved further. The assessment of antimicrobial susceptibility tests is interpreted based on CLSI Criteria.

Quality control for antimicrobial susceptibility tests depends on medical institutions. To improve the quality of antimicrobial susceptibility tests at hospital laboratories, a quality control program was developed under the leadership of the Japanese Society for Clinical Microbiology and it has been piloted since 2016.

JANIS is a surveillance program regulated by the Statistics Act and it differs from the National Epidemiological Surveillance of Infectious Diseases based on the Infectious Diseases Control Act. While participation is voluntary, from 2014, Premiums for infection control 1 in medical reimbursement requires participation in JANIS or equivalent surveillance programs. JANIS is organized and operated by the Ministry of Health, Labour and Welfare, and its operating policy is determined at the operation council that comprises of experts in infectious diseases, antimicrobial resistance and other relevant professional fields. Section II, Laboratory of Antimicrobial Resistance Surveillance, National Institute of Infectious Diseases functions as a secretariat office for JANIS.

Under the Global Antimicrobial Resistance Surveillance System (GLASS), launched by WHO in 2015, individual countries are encouraged to submit data regarding resistant bacterias in the human health area.[1] Japan has provided necessary data from JANIS and other pertinent monitoring systems to GLASS. Of note, data for 2014 to 2020 have already been submitted. GLASS is calling for the same set of antimicrobials to be used in antimicrobial susceptibility tests at medical institutions subject to monitoring in each country. As JANIS is a voluntary surveillance program, it collects whatever data can be supplied by the participating medical institutions, in whatever form that data emerges from the institutions' routine testing operations. Standardizing the types of antimicrobials tested is therefore difficult. For this reason, JANIS data is collected separately from the regular data, and only data on strains for which susceptibility tests are conducted for all the agents designated by GLASS are extracted and tabulated, and the tabulated results are submitted to GLASS. Techniques for compiling data are being considered as part of the JANIS program, to facilitate international cooperation in surveillance. Under GLASS, the expansion of the scope of surveillance to food-producing animal and other areas are discussed.[1] It is expected that the data from this national one health report can be contributed to GLASS.

2) Methods for submission

JANIS consists of five divisions: (1) Clinical Laboratory, (2) Antimicrobial-Resistant Bacterial Infection, (3) SSI, (4) ICU and (5) NICU. Medical institutions select divisions to participate in, in accordance with their purposes and conditions. Among the five divisions, Clinical Laboratory division handles surveillance regarding antimicrobial resistance. In Clinical Laboratory division, all data concerning isolated bacteria are collected from bacteriological examination units installed in the laboratories of medical institutions, computerized systems, and other sources, and converted into the JANIS format before submitted online. The submitted data are aggregated, and the shares of clinically important bacterial species that are resistant to key antimicrobials are calculated, and published as the national data of Japan.

3) Prospects

Most medical institutions participating in JANIS are of a relatively large scale with 200 or more beds. Data are not collected from clinics. The bias based on this sampling policy in JANIS should be addressed.

(2) National Epidemiological Surveillance of Infectious Disease (NESID)

1) Overview

The NESID program collects and publishes domestic information regarding infectious diseases, and monitors the occurrence of and trends in infectious diseases, based on reports from physicians and veterinarians. At present, the NESID program is conducted in accordance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (hereinafter referred to as "Infectious Diseases Control Law"), which took effect in April 1999. The goal of NESID is to accurately identify and analyze information regarding the occurrence of infectious diseases and to rapidly provide and publish the results to the general public and healthcare practitioners, thereby promoting measures for the effective and adequate prevention, diagnosis and treatment of infectious diseases, and preventing the occurrence and spread of various infectious diseases, while verifying the detection status and characteristics of circulating pathogens, and facilitating appropriate infection control measures, through the collection and analysis of pathogen information.

As of July 2019, the following seven antimicrobial-resistant bacteria infections are designated as reportable under NESID, which are all classified as Category V Infectious Diseases. The four diseases that are subject to notifiable disease surveillance, which requires reporting by all physicians, are vancomycin-resistant enterococcal infection (VRE, designated in April 1999), vancomycin-resistant *Staphylococcus aureus* infection (VRSA, designated in November 2003), carbapenem-resistant *Enterobacteriaceae* infection (CRE, designated in September 2014), and multiagent-resistant *Acinetobacter* infection (MDRA, designated as a disease reportable from designated sentinel sites in February 2011, and changed to a disease reportable under notifiable disease surveillance in September 2014). The three diseases that are reportable from approximately 500 designated sentinel sites (medical institutions that have 300 or more beds, with internal medicine and surgery departments) across Japan are penicillin-resistant *Streptococcus pneumoniae* infection (PRSP, designated in April 1999), methicillin-resistant *Staphylococcus aureus* infection (MRSA, designated in April 1999), and multiagent-resistant *Pseudomonas aeruginosa* infection (MDRP, designated in April 1999).

2) Reporting criteria

A physician who has diagnosed a reportable disease listed above (the manager of a designated notification facility in the case of a disease subject to sentinel surveillance) should report to a Public Health Center using a designated reporting form. The scope of reporting includes cases where bacteria that satisfy the laboratory findings specified in Table 101 are detected, and the isolated bacteria are regarded as the cause of the relevant infectious disease, or cases where it was detected from specimens that normally should be aseptic. Carriers are excluded from the scope of reporting.

Table 101. Reporting criteria

Reportable disease	Summary of reporting criteria
VRE	*Enterococcus* is isolated and identified, and the MIC value of vancomycin is ≥ 16 μg/mL.
VRSA	*Staphylococcus aureus* is isolated and identified, and the MIC value of vancomycin is ≥ 16 μg/mL.
CRE	*Enterobacteriaceae* is isolated and identified, and either A) or B) below is satisfied: A) The MIC value of meropenem is ≥ 2 μg/mL, or the diameter of the inhibition circle of the meropenem susceptibility disk (KB) is ≤ 22 mm. B) It is confirmed that both the following conditions are satisfied: a) The MIC value of imipenem is ≥ 2 μg/mL, or the diameter of the inhibition circle of the imipenem susceptibility disk (KB) is ≤ 22 mm. b) The MIC value of cefmetazole is ≥ 64 μg/mL, or the diameter of the inhibition circle of the cefmetazole susceptibility disk (KB) is ≤ 12 mm.
MDRA	MDRA *Acinetobacter* spp. is isolated and identified, and all three conditions below are satisfied: A) The MIC value of imipenem is ≥ 16 μg/mL, or the diameter of the inhibition circle of the imipenem susceptibility disk (KB) is ≤ 13 mm. B) The MIC value of amikacin is ≥ 32 μg/mL, or the diameter of the inhibition circle of the amikacin susceptibility disk (KB) is ≤ 14 mm. C) The MIC value of ciprofloxacin is ≥ 4 μg/mL, or the diameter of the inhibition circle of the ciprofloxacin susceptibility disk (KB) is ≤ 15 mm.
PRSP	*Streptococcus pneumoniae* is isolated and identified, and the MIC value of penicillin is ≥ 0.125 μg/mL, or the diameter of the inhibition circle of the oxacillin susceptibility disk (KB) is ≤ 19 mm.
MRSA	*Staphylococcus aureus* is isolated and identified, and the MIC value of oxacillin is ≥ 4 μg/mL, or the diameter of the inhibition circle of the oxacillin susceptibility disk (KB) is ≤ 10 mm.
MDRP	*Pseudomonas aeruginosa* is isolated and identified, and all three conditions below are satisfied: A) The MIC value of imipenem is ≥ 16 μg/mL, or the diameter of the inhibition circle of the imipenem susceptibility disk (KB) is ≤ 13 mm. B) The MIC value of amikacin is ≥ 32 μg/mL, or the diameter of the inhibition circle of the amikacin susceptibility disk (KB) is ≤ 14 mm. C) The MIC value of ciprofloxacin is ≥ 4 μg/mL, or the diameter of the inhibition circle of the ciprofloxacin susceptibility disk (KB) is ≤ 15 mm.

3) System

Public Health Centers confirm reported information, and enter the data into NESID. The registered information is further confirmed and analyzed, and additional information is collected, by local infectious disease surveillance centers, the Infectious Diseases Surveillance Center of NIID as the central infectious disease surveillance center, and other relevant bodies. Patient information (e.g. the reported numbers of patients, and trends) that is collected under the Infectious Diseases Control Law, and other related information, are provided to the general public through the Infectious Diseases Weekly Reports (IDWRs) and other media. A March 2017 notification issued by the Director of the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW imposed on local public health institutes and other organizations a requirement to test strains isolated from notified cases of CRE infection. Since then, data concerning the detection of major carbapenemase genes in strains isolated from notified cases of CRE infection have been collected and analyzed within the framework of the monitoring of trends in outbreaks of infection and have been published in the Infectious Agents Surveillance Report (IASR), among others.

4) Prospects

A certain level of quality is considered to be guaranteed in the reporting of antimicrobial-resistant bacteria infections under NESID, since reporting is based on case definitions specified by the Infectious Diseases Control Law. Although cases may be underestimated in notifiable disease surveillance, an overall picture of trends in occurrence can be monitored. This surveillance system is also considered useful because, when an unusual trend is observed, it may trigger an intervention (e.g. investigation, guidance) at the relevant medical institution by the Public Health Center. Trends in diseases reportable from designated sentinel sites have been recorded since the launch of the NESID program in 1999, and considered useful for monitoring medium- to long-term trends in the occurrence of the target diseases. In addition, pathogen surveillance focused primarily on CRE was launched in 2017 and, with data on resistance genes set to be gathered and analyzed for VRE and MDRA in due course, it is anticipated that information that will be valuable in devising measures to combat antimicrobial-resistant bacteria will be collected and utilized.

(3) Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)

1) Overview

In 2017, the governance of the Regional Infection Control Support System (RICSS) was transferred to the AMR Clinical Reference Centre to utilize the system for AMR control as a surveillance platform for infection control at regional as well as national levels. The system was renamed to Japan Surveillance for Infection Prevention and Healthcare Epidemiology: J-SIPHE).

The system has been launched as a system that can be utilized for AMR measures in hospitals as well as for the promotion of regional cooperation, a large amount of data has been accumulated, and an annual report is published annually to return the data to the facilities using the system. The J-SIPHE 2021 Annual Report covers a total of 818 participating medical institutions.

The system is designed to collect information on the status of infectious disease treatment, infection control measures and the appropriate use of antimicrobials, the occurrence of healthcare-associated infections, the occurrence of major bacteria and drug-resistant bacteria, the occurrence of bloodstream infections caused by them, and the use of antimicrobials at participating facilities, and to make the use of this information at the facilities themselves and in regional networks. With these as its purpose, the system also serves to establish indicators for AMR control.

2) System

This system is based on participation in a regional cooperation network within the framework of the medical fee premium for infection prevention measures. In order to support AMR measures by utilizing the regional cooperation network, etc., information can be shared within the group based on unified standards, and the system visualizes data that are necessary and adequate for AMR measures by making secondary use of existing information such as returned JANIS laboratory section data and integrated inpatients EF files, while reducing the burden on participating facilities.

3) Prospects

At present, the system is mainly used by facilities with a relatively large number of beds and of the Infection Prevention and Control Premium 1 category and it needs to be upgraded to be more in line with regional cooperation, easier to use for facilities with limited infection control human resources, and more meaningfully useful in regional cooperation conferences, etc. The system aims to be more effectively used in building infection control networks at the regional level and in decision-making on infection control.

(4) Trend surveillance of antimicrobial-resistant Mycobacterium tuberculosis

1) Overview

registered tuberculosis patient information system is a part of NESID including: new tuberculosis patients and latent tuberculosis patients who are registered from January 1 to December 31 of a registration year; and all tuberculosis patients who are registered as of December 31 of the calendar year. In principle, information in this system pertains to tuberculosis patients, and focuses on the number of incidence case and incidence rate, the number of patients with tuberoses, treatment status, the number of deaths from tuberculosis, and so on. Information regarding tuberculosis bacillus as the causal bacteria is limited to the smear positive ratio, the number of culture-positive patients, agent-susceptibility testing data, and so on. Though limited, this report exclusively provides routine national information regarding antimicrobial-resistant tuberculosis bacillus.

2) Survey methods

Based on the registered tuberculosis patient information, the results of agent-susceptibility testing in newly registered patients with culture-positive pulmonary tuberculosis are aggregated. The entry of this information item used to be optional, before the Ordinance for the Partial Revision of the Enforcement Regulation of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (MHLW Ordinance No. 101 of 2015, effective May 21, 2015) added "the results of agent-susceptibility testing" under "Conditions of disease" in Item 4, Paragraph 1, Article 27-8.

3) System

When physicians diagnose and report a tuberculosis case to Public Health Center collect, corresponding public health nurses collect detailed information from patients and physicians. Agent-susceptibility testing data are considered to be collected mostly from hospital and commercial laboratories. Those individual data are entered by Public Health Centers across Japan into NESID.

4) Prospects

The surveillance based on the registered tuberculosis patient information system contains the susceptibility results of newly registered patients with culture-positive pulmonary tuberculosis, as reported from all medical institutions. Therefore, data are considered nationally representative. Improvement in the entry rate of agent-susceptibility testing results (approximately 80% at present); the establishment of a system for nationwide quality assurance for agent-susceptibility testing; and the quality control of data entry are warranted.

(5) Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

1) Overview

JVARM is a nationwide system for monitoring antimicrobial-resistant bacteria among animals. This monitoring has been conducted by the Ministry of Agriculture, Forestry and Fisheries since 1999 through its network of connections with livestock hygiene service centers across Japan. JVARM provides globally important information and is cited as an example of a monitoring system in the WHO report “Antimicrobial resistance: global report on surveillance 2014.”

Under JVARM, three types of monitoring are conducted: (1) monitoring of the volumes of use of antimicrobials (estimated from the volumes of sales); (2) monitoring of antimicrobial resistance among indicator bacteria and foodborne pathogens derived from healthy animals; and (3) monitoring of antimicrobial resistance in pathogenic bacteria (clinical isolates) derived from diseased animals. While verifying the efficacy of veterinary antimicrobials, JVARM also provides basic data for risk assessment and risk management concerning antimicrobial resistance, taking into account influence on human healthcare (Figures 4). The results of JVARM are published on the website of the National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries [2]. In FY2016, reviews were carried out to consider how to strengthen antimicrobial resistance surveillance in aquatic animals and how to conduct antimicrobial resistance surveillance in companion animals, in accordance with the strategies of the National Action Plan on AMR. Antimicrobial resistance surveillance in diseased dogs and cats was launched in FY2017 and in healthy dogs and cats in FY2018. In FY2021, discussion about methodologies for antimicrobial resistance monitoring in the livestock environment started.

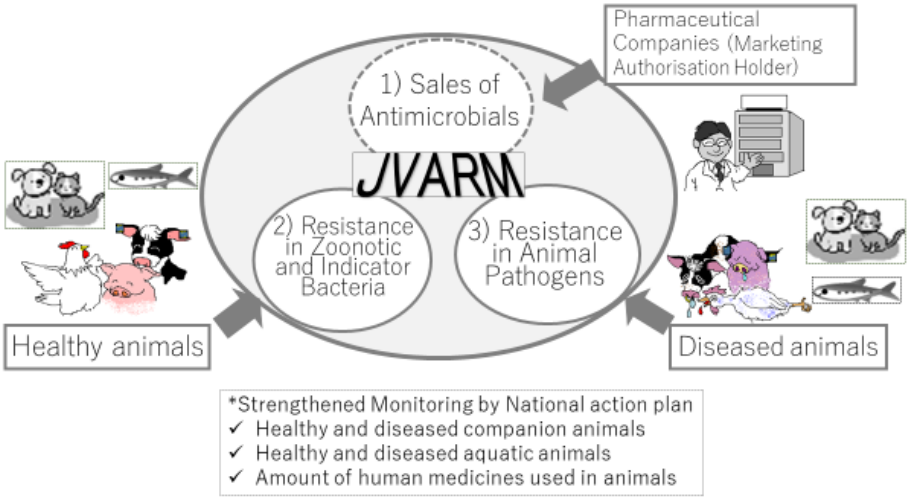


Figure 4. Overview of veterinary antimicrobial resistance monitoring

2) System for the antimicrobial resistance monitoring

When JVARM first began, surveillance of foodborne pathogenic bacteria and indicator bacteria from healthy animals was carried out using samples of strains isolated and identified from the feces of food-producing animals collected at farms by livestock hygiene service centers. Surveillance using strains isolated and identified by the contracted testing agency from feces collected at animal and poultry slaughterhouses was launched in FY2012, as this facilitated more intensive sampling at a stage closer to the final food product. In FY2016, as it had been confirmed that there was no major difference in the findings of both surveys, JVARM shifted completely from sampling at farms to sampling at animal and poultry slaughterhouses (Figure 5). Bacteria were isolated from faecal samples collected from slaughterhouses (five sites nationwide) and poultry slaughterhouses (13 sites nationwide), using species-selective media, and data are based on one strain per bacterial species per farm (the farm's representative strain).

In the case of clinical isolates from food-producing animals, bacterial strains isolated and identified from materials for pathological appraisal by livestock hygiene service centers across the country were collected. One or two strains isolated from a different individual affected in a single case of infectious disease were collected for the monitoring. The MIC values for these strains are measured by the National Veterinary Assay Laboratory using a broth microdilution method based on the CLSI Criteria (Figure 5). The scope of antimicrobial monitoring includes a broad range of active ingredients that are considered important in antimicrobials used exclusively for animals, antimicrobials used for both animals and humans, and antimicrobial feed additives, among others. Antimicrobial agents subject to monitoring are selected for each bacterial species, according to the past monitoring results and Chapter 6.8 of the WOAH Terrestrial Animal Health Code.[3]

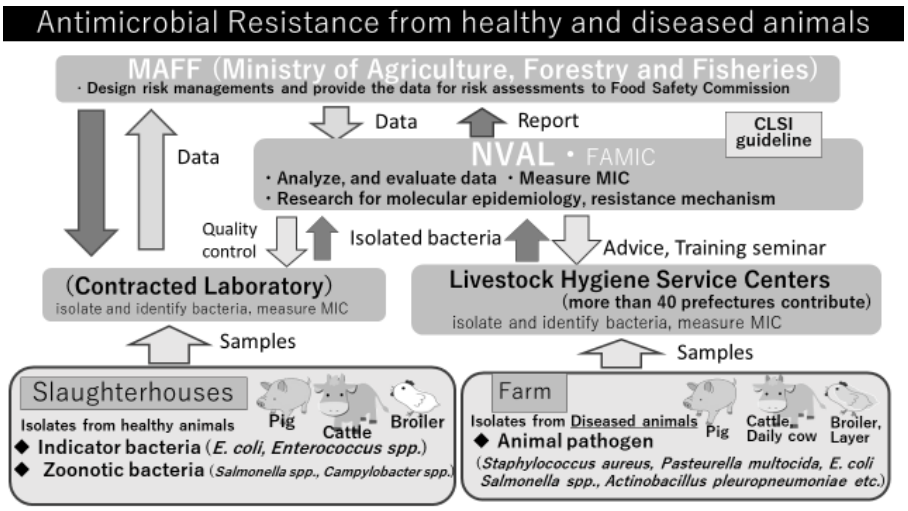


Figure 5. Monitoring system for drug-resistant bacteria from healthy livestock (slaughterhouses and poultry slaughterhouses) and from diseased livestock (farms).

For the companion animal survey, the survey method was determined based on the results of the discussion at the Working Group on Companion Animal AMR Surveillance, and from 2017, strains derived from diseased dogs and cats were collected from clinical laboratories. Also, from 2018, healthy dogs and cats were targeted, and specimens were collected from veterinary hospitals nationwide with the cooperation of the Japan Veterinary Medical Association (Fig. 6).

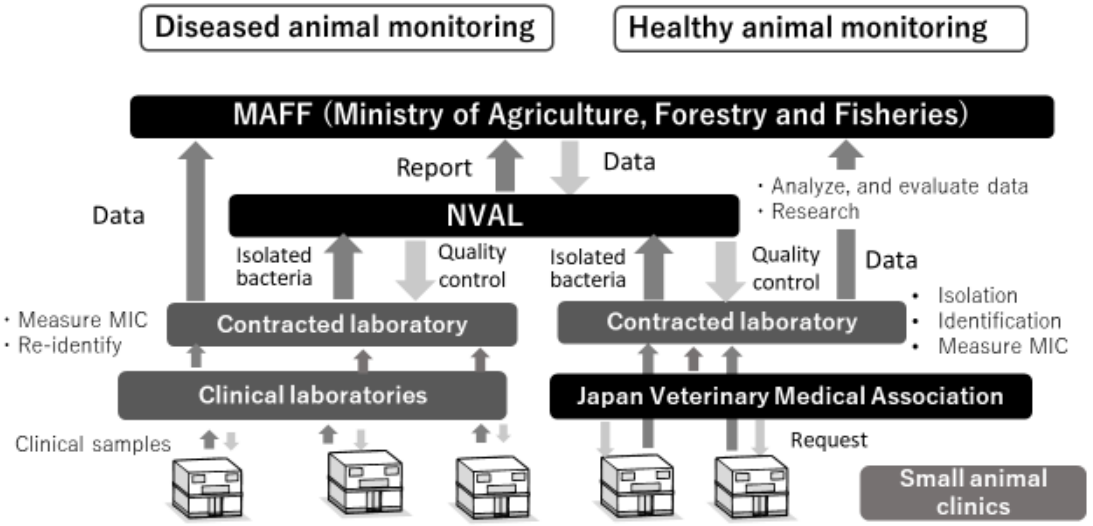


Figure 6. System for antimicrobial resistance monitoring in healthy and diseased dogs and cats

Isolation of bacteria from specimens was carried out using selective media in all cases, with one strain of one species per hospital. The MICs of the collected strains were determined at the contract laboratory using the micro-liquid dilution method according to CLSI. Antimicrobial substances to survey were selected for each species of bacteria, taking into account the drugs used in clinical settings for companion animals in addition to those targeted in the livestock survey.

Efforts are made to achieve standardization in the isolation and identification of strains and antimicrobial susceptibility testing, by such means as training sessions for the staff of livestock hygiene service centers who carry out this work at the National Veterinary Assay Laboratory each year and checks of quality control at the contracted testing agency. In addition, a parallel survey of the origin of the samples and the date on which they were collected is carried out. Isolated strains collected under JVARM are examined and stocked by the National Veterinary Assay Laboratory, which also performs the analysis of genetic properties and the clarification of antimicrobial resistance mechanism, in order for the molecular epidemiological survey of antimicrobial-resistant strains. Antimicrobial feed additives are analyzed by the FAMIC. Data collected through JVARM are published on the website of the National Veterinary Assay Laboratory every year. The data are also utilized for risk assessment by the Food Safety Commission as well as for science-based risk management measures.

In addition, since 2012, JVARM has been collaborating with JANIS, which monitors drug-resistant bacteria in human medical settings, to convert data on E. coli from healthy livestock collected by JVARM into a format that can be compared with JANIS data and publish the results as an antibiogram on the National Veterinary Assay Laboratory's website. This enables the comparison of trends in drug-resistant bacteria between humans and animals.[5]

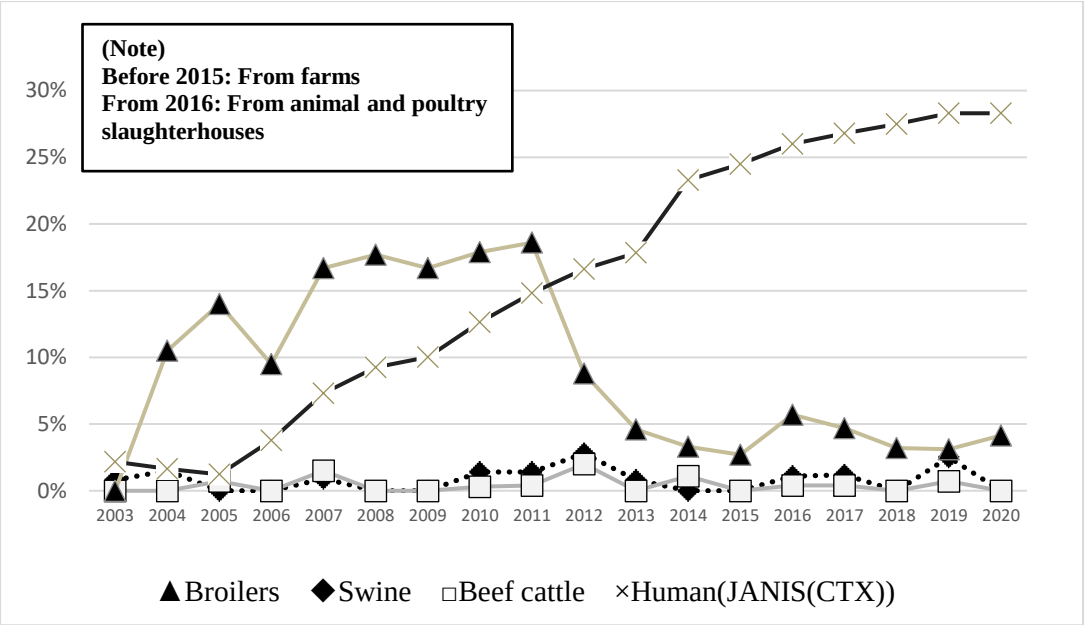


Figure 7. Comparison of the proportion of third-generation cephalosporin-resistant *Escherichia coli* derived from humans and food-producing animal

The resistance rate to third-generation cephalosporins had increased until 2011 in both human-derived and broiler -derived *E. coli*, but then has decreased drastically in broiler since 2012. This may be due to the discontinuation of the off-label use of third-generation cephalosporins, which had been practiced in some egg hatcheries, in response to the guidance given to the relevant organizations advising to stop it by presenting the JVARM results. [6] In humans, on the other hand, the rate has continued to increase, showing different trends in humans and broiler (Figure 7).

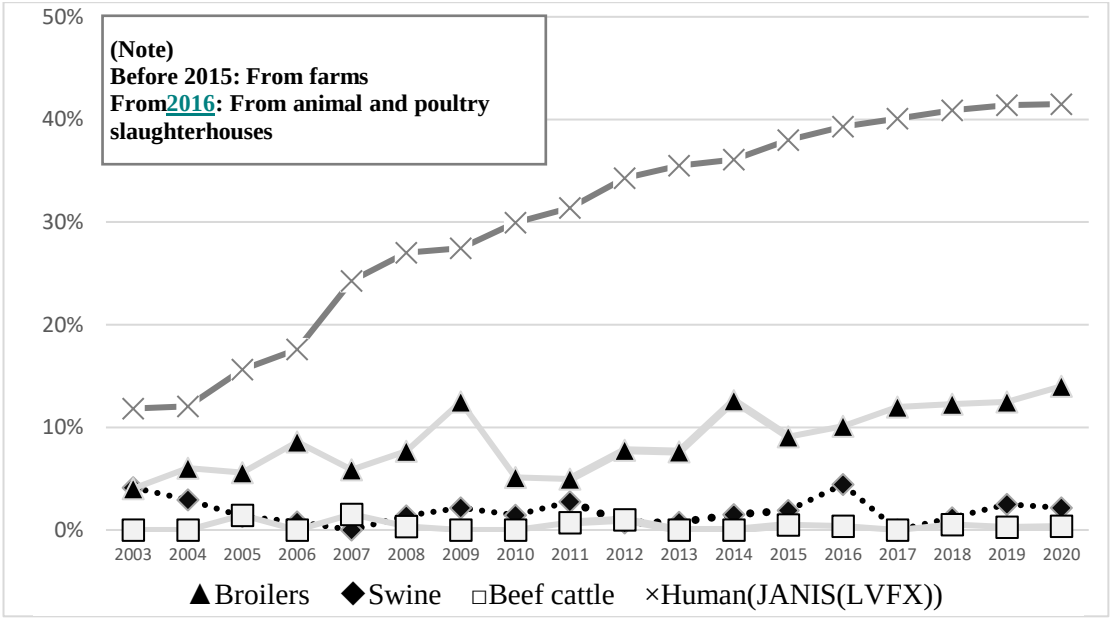


Figure 8. Comparison of the proportion of fluoroquinolone-resistant *Escherichia coli* derived from humans and food-producing animal

While an increasing trend in the fluoroquinolone resistance rate of human *E. coli* has been consistently observed since 2003, the fluoroquinolone resistance rate of E. coli from livestock has remained below 5% for swine and beef cattle-derived strains and below 15% for broiler-derived strains, showing different trends between human and livestock (Figure 8)

3) Monitoring on the sales volumes of antimicrobials

An annual monitoring is conducted on the volumes of sales of veterinary antimicrobials, based on the reported quantities of veterinary agents handled by marketing authorization holders, pursuant to Article 71-2 of the Veterinary Agent Control Regulations (MAFF Ordinance No. 107 of 2004) (Figure 9). Starting 2001, the monitoring has included the volume of sales by active pharmaceutical ingredient, and the estimated percentage of sales by animal species, in addition to the volumes of sales by antimicrobial class and route of administration. The data are aggregated and published on the website of the National Veterinary Assay Laboratory as "Annual Report of Sales Amount and Sales Volume of Veterinary agents, Quasi-agents and Medical Devices." Under the WOAH Terrestrial Animal Health Code's section on antimicrobial usage (Chapter 6.9), [4] these data are submitted to the WOAH for the activity to understand and compare usage in each country of the world.

Figure 9. Monitoring on the sales volumes of antimicrobials

4) Future prospects

The main issues to be addressed by JVARM in the future are: 1) further promotion of more advanced investigation and analysis of ARGs through whole-genome analysis of bacteria from livestock and companion animals, and consideration of their use in trend surveys and comparison with the human field; 2) evaluation of the amount of veterinary antimicrobial use with reference to biomass weights calculated by the standardized technique set out by the WOAH; and 3) establishing and implementing methodology to investigate the distribution of antimicrobial-resistant bacteria in the environment around livestock production sites. While continuing to carry out the monitoring already implemented in the veterinary field, JVARM will begin efforts to address these issues. Furthermore, to promote the One Health surveillance and monitoring, we will continue to enhance our collaboration with JANIS, for example by comparing whole-genome analysis data. Those data accumulated will lay the ground for risk assessment and risk management by clarifying the transmission process of antimicrobial resistance bacteria through collaborating with other fields.

(6) Trend Surveillance of Antimicrobial Agents in Japan (JSAC, J-SIPHE)

1) Overview

The governance of Japan Antimicrobial Consumption Surveillance (JACS), an antimicrobial use surveillance system established in 2015 through the Ministry of Health, Labour and Welfare (MHLW) Science Research, was transferred to the AMRCRC, and it was renamed to Japan Surveillance of Antimicrobial Consumption (JSAC) (Antimicrobial Use Surveillance) in 2022 in order to conduct a monitoring of antimicrobial use in humans in Japan on an annual and continuous basis at national level and utilize it in AMR measures. Currently, JSAC (http://amrcrc.ncgm.go.jp/surveillance/index.html) investigates antimicrobials use (AMU) in humans in overall Japan and by prefecture using sales volume information and NDB. In addition, AUDs and DOTs of each participating facility are compiled and published as an annual report in J-SIPHE (https://j-siphe.ncgm.go.jp/).

2) Monitoring methods

The sales volume data is used to calculate the potency for each agent for overall use and by dosage form (oral and parenteral) and by prefecture, and figures are collated based on either the ATC or AWaRe classification advocated by the WHO. In the case of AMU in humans, these figures are shown over time, adjusted by defined daily dose (DDD) as defined by the WHO, then adjusted by population to calculate DID (DDDs/1,000 inhabitants/day). To monitor AMU from a One Health perspective, figures converted into titer values are summarized by weight for each ATC category and are then shown totaled with AMU elsewhere. Figures shown for AMU at medical institutions are the results from J-SIPHE monitoring.

* ATC Classification: Anatomical Therapeutic Chemical Classification System, a classification system for pharmaceutical products proposed by WHO.
* AWaRe classification: an indicator of appropriate antimicrobial use recommended by WHO (see p. 86)

3) Prospects

The establishment of Japan's first AMU surveillance programs in the form of JSAC and J-SIPHE put in place a system that enables trends in AMU over time to be fed back to the public. Sources of AMU information include both data on the volume of sales and insurance billing data. The sources of information used and the way in which they are presented need to be altered according to their purpose and further consideration is required regarding the form in which they should be collated and fed back on an ongoing basis.

(7) Monitoring on the antimicrobial-resistant Campylobacter spp. isolated from humans

1) Overview

Currently the monitoring regarding the emergence of antimicrobial-resistant *Campylobacter* spp. derived from humans is undertaken as research activities by the Tokyo Metropolitan Institute of Public Health, as part of the food safety assurance and promotion research project, with grants for research from the Ministry of Health, Labour and Welfare of Japan.[9]

2) Survey methods

Antimicrobial susceptibility tests were conducted by the disk method, in accordance with the CLSI standards in US.[9] 86 *Campylobacter jejuni* and 7 *Campylobacter coli* strains isolated from faeces of diarrhoea patients at hospitals in Tokyo in 2020 were tested using five antimicrobials such as ABPC, TC, NA, CPFX, and EM. Results were determined by measuring the zone of inhibition and following the susceptibility determination table in the protocol[9].

3) Prospects

To identify the emergence of antimicrobial-resistant *C. jejuni /C. coli* on a wide-area basis, it is required to standardize tested antimicrobials, implementation methods, assessment criteria, and other details. While tests were conducted using the disk method, in accordance with U.S. CLSI standards, judgment criteria are provided for only three agents, namely CPFX and EM. Accordingly, other agents were assessed in accordance with standards unified as part of a Ministry of Health, Labour and Welfare-funded research project concerning the promotion of food safety, with reference to EUCAST breakpoints and various literature. It is required to conduct antimicrobial susceptibility tests using common methods not only for strains isolated from humans, but also for strains isolated from food, in order to know the emergence of antimicrobial-resistant bacteria nationwide.

(8) Monitoring on the antimicrobial-resistant non-typhoidal *Salmonella* spp. isolated from humans and from food

1) Overview

Many Public Health Institutes conducted resistance monitoring regarding antimicrobial-resistant bacteria derived from food. Several Public Health Institutes were organized to undertake the monitoring of antimicrobial-resistant bacteria derived from food as research activities, as part of the food safety assurance and promotion research project, with Grants for research from the Ministry of Health, Labour and Welfare of Japan.[10] This is likely the first monitoring in Japan regarding antimicrobial-resistant bacteria derived from food on a nationwide scale, conducted by standardized methods. The collected data were also reported to GLASS, which was launched by WHO.

2) Methods

With cooperation from 21 Public Health Institutes across Japan, an antimicrobial resistance monitoring was conducted using the common protocol, antimicrobials, instruments, etc., concerning bacteria, particularly *Salmonella* spp., derived from human patients and from food, as collected by these Public Health Institutes.[10] The monitoring was targeted at *Salmonella* spp. strains that were isolated from human patients and from food in 2015 and 2021. Strains derived from humans included those isolated from specimens of patients with infectious gastroenteritis or with food poisoning. For each strain derived from food, the type of source food and the date of isolation were identified. When the source food was chicken meat, information was collected concerning the country of production (domestic, imported (country name), and unknown). The 21 cooperating Public Health Institutes performed antimicrobial susceptibility tests by the CLSI disk diffusion method, in accordance with the Public Health Institute Group Protocol for Antimicrobial Susceptibility Tests, using strains that were assessed as *Salmonella* spp. The susceptible discs were ampicillin (ABPC), gentamicin (GM), kanamycin (KM), streptomycin (SM), tetracycline (TC), ST combination agent (ST), chloramphenicol (CP), cefotaxime (CTX), ceftazidime (CAZ), and cefoxitin (CFX), fosfomycin (FOM), nalidixic acid (NA), ciprofloxacin (CPFX), norfloxacin (NFLX), amikacin (AMK), imipenem (IPM) and meropenem (MEPM) 17 agent discs were used. All Public Health Institutes used common reagents (e.g. susceptibility disks) and instruments (e.g. disk dispensers, vernier calipers) for the tests. Susceptibility disks were laid out on an agar plate as indicated in the layout drawing in the protocol, so that inhibition circles would not be coalesced. The zone of inhibition was measured, and the measurements were assessed based on the susceptibility assessment chart in the protocol.

3) Prospects

Clear similarity was observed in the proportion of antimicrobial-resistant strains derived from humans and of those derived from food. As these data are vital to the One Health approach, which covers the environment, animals, food, and humans, a system has been established that uses conversion software to integrate the data with JANIS and JVARM data to facilitate integrated evaluation of all three.

(9) Monitoring on the antimicrobial-resistant Neisseria gonorrhoeae

1) Overview

In the diagnosis of gonococcal infection, the utilization of nucleic acid testing has been promoted. Isolation culture is only implemented for some patients. Because antimicrobial susceptibility tests for *Neisseria gonorrhoeae* cannot be easily implemented in general laboratories or laboratory companies, it is difficult for JANIS to monitor trends in these bacteria. Therefore, a monitoring on the antimicrobial-resistant *Neisseria gonorrhoeae* has been undertaken as research activities at AMED since 2015. The collected data are also reported to GLASS, which is operated by WHO.

2) Survey methods

More than 40 cooperating clinics are designated across Japan. Antimicrobial susceptibility tests were performed at five facilities capable of testing across Japan, after collecting specimens from the cooperating clinics, or collecting strains through laboratory companies. Antimicrobial susceptibility tests were performed using an agar plate dilution method, recommended by CLSI or EUCAST, or using Etest. MIC values were measured for CTRX and spectinomycin as recommended agents; for AZM, which was used as part of the two-agent combination therapy overseas; and for PCG, CFIX, and CPFX, which had been used as recommended agents in the past. The EUCAST standards were used for susceptibility and resistance assessment (Table 102). For reference, the proportion of resistant strain based on CLSI Guidelines (M100- S25) (Table 104) is indicated in Table 104. The figures for AZM in the tables are based on the MIC distribution of strains that have antimicrobial-resistant gene, as indicated by CLSI Guideline (M100-S27).

3) Prospects

Physicians need to empirically choose therapeutic agents for gonococcal infection according to the result of the monitoring given the difficulty in routinely performing antimicrobial susceptibility tests.

For empiric treatment, it is recommended to use an agent with the potential success rate of 95% or higher. At present, ceftriaxone and spectinomycin are the only recommendable agents in Japan. Because *Neisseria gonorrhoeae* that are present in the pharynx are an important source of infection, *Neisseria gonorrhoeae* in pharynx should be treated. Due to its *in vivo* pharmacokinetics, spectinomycin does not have effect on *Neisseria gonorrhoeae* present in the pharynx. Therefore, ceftriaxone is the only practically recommendable agent.

In sporadic cases, strains isolated in Japan indicate the ceftriaxone MIC of 0.5 μg/mL in antimicrobial susceptibility tests. Ceftriaxone is administered by intramuscular injection overseas, and therefore subject to dose limitation. Therefore, if strains that indicate the ceftriaxone MIC of 0.5 μg/mL are transmitted to overseas, it is likely that ceftriaxone loses its effect. Hence, it is required to continue with the careful monitoring of isolated strains in coming years. Reports of the isolation of strains with the same resistance gene as the resistant strain isolated in Osaka in 2015 [7] have been received from across the globe since 2017.[8]

Table 102. Antimicrobial susceptibility assessment criteria based on EUCAST (μg/mL) for *Neisseria gonorrhoeae*

	Susceptible		Resistant
PCG	≤ 0.06	0.125–1	> 1
CFIX	≤ 0.125	-	> 0.125
CTRX	≤ 0.125	-	> 0.125
SPCM	≤ 64	-	> 64
AZM	≤ 0.25	0.5	> 0.5
CPFX	≤ 0.03	0.06	> 0.06

Table 103. Antimicrobial susceptibility assessment criteria based on CLSI (μg/mL) for *Neisseria gonorrhoeae*

	Susceptible		Resistant
PCG	≤ 0.06	0.125–1	≧ 2
CFIX	≤ 0.25	-	-
CTRX	≤ 0.25	-	-
SPCM	≤ 32	64	≧ 128
AZM*	-	-	-
CPFX	≤ 0.06	0.12-0.5	≧ 1

* Epidemiological cutoff value indicated in CLSI Standards (M100-S27): wild type (WT) ≤ 1; non-WT ≥ 2

Table 104. The proportion (%) of antimicrobial-resistant *Neisseria gonorrhoeae* based on the CLSI (M100-S25)

	2015	2016	2017
CTRX[$]	0.6	0.4	0.5
SPCM	0	0	0
AZM*	3.2	4.0	4.0
PCG[†]	36.0 (96.1)	35.8 (96.7)	37.8 (99.0) [†]
CFIX[$]	16.1	11.0	10.0
CPFX[†]	79.0 (79.4)	77.9 (78.3)	74.2 (75.8)

[$] Non-susceptibility rate

* The figures are based on the epidemiological cutoff value (non-WT ≥ 2 μg/mL) indicated in CLSI Standards (M100-S27), and differ from resistance proportion.

[†]*Figures in parentheses indicate the sum of resistance and intermediate resistance.

(10) Monitoring on the antimicrobial-resistant *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Shigella* spp.

1) Overview

For typhoid and paratyphoid fever, and shigellosis, definitive diagnosis is undertaken based on bacterial isolation. Given there is no routine antimicrobial resistance monitoring regarding *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Shigella* spp., susceptibility tests are performed at the National Institute of Infectious Diseases, using strains submitted based on the Notification for Epidemiological Surveillance. Antimicrobial resistance information concerning *Shigella* spp. is also used as data reported to GLASS.

2) Methods

Antimicrobial susceptibility tests are performed using strains that are submitted based on the Notification for Epidemiological Surveillance (HSB/TIDCD Notification No. 100901, PFSB/ISD Notification No. 100902). In antimicrobial susceptibility tests, assessment was performed in accordance with CLSI standards, using a broth microdilution method for *Salmonella* Typhi and *Salmonella* Paratyphi A, and using a disk diffusion method for *Shigella* spp.

3) Prospects

Treatment with antimicrobials is essential for typhoid and paratyphoid. To enable the proper selection of effective therapeutic agents, it is necessary to conduct continuous monitoring. The proportion of strains that are resistant to quinolones and other commonly used antibacterials are high in *Shigella* spp., and therefore recurrence is also possible even after administering antimicrobials. Careful monitoring is required to prevent possible spread of infection in Japan.

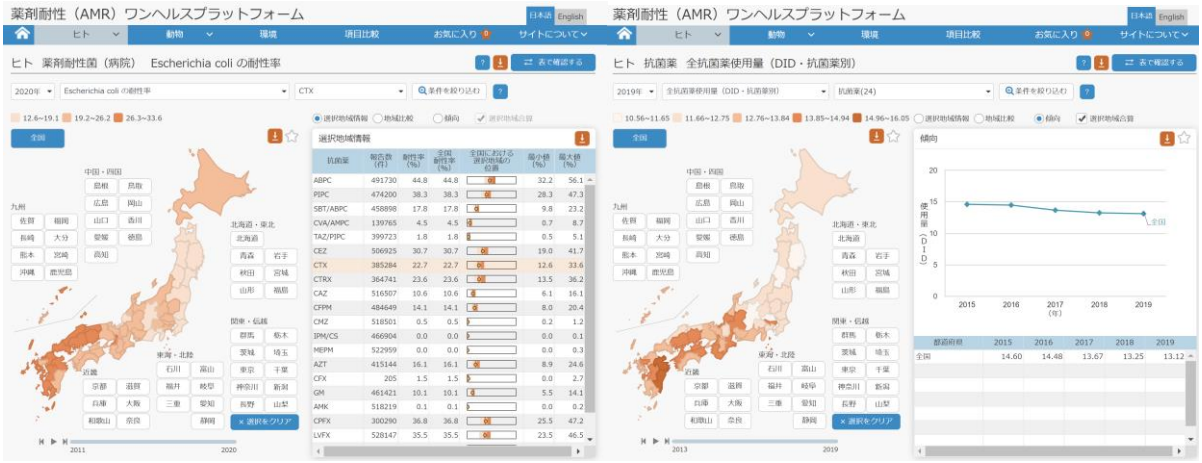
(11) Antimicrobial Resistance (AMR) One Health Platform

1) Overview

In October 2019, the AMRCRC published the “Antimicrobial Resistance (AMR) One Health Platform" （https://amr-onehealth-platform.ncgm.go.jp/home）, a website that provides easy-to-understand information related to infectious diseases in the human, animal and environmental fields.

This system allows users to freely view trends in agent resistance rates, antimicrobial use, and other AMR-related indicators by field, prefecture, and year. The information handled is mainly secondary use from outputs of this report, AMED research and other deliverables.

In November 2021, prefectural homepage was newly established, which allows users to view various indicators in one place from the homepage of each prefecture. We hope that this platform will be utilized to further promote AMR measures in each region.



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Websites of Key Trend Surveys

AMR Clinical Reference Center

http://amrcrc.ncgm.go.jp/

Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)

https://j-siphe.ncgm.go.jp/

Nippon AMR One Health Report

https://amr-onehealth.ncgm.go.jp/

Antimicrobial Resistance (AMR) One Health Platform

https://amr-onehealth-platform.ncgm.go.jp/home

Japan Surveillance of Antimicrobial Consumption (JSAC)

http://amrcrc.ncgm.go.jp/surveillance/index.html

Japan Nosocomial Infections Surveillance (JANIS), Ministry of Health, Labour and Welfare

https://janis.mhlw.go.jp/

National Epidemiological Surveillance of Infectious Disease (NESID)

https://www.niid.go.jp/niid/ja/allarticles/surveillance/2270-idwr/nenpou/6980-idwr-nenpo2015.html

Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

http://www.maff.go.jp/nval/yakuzai/yakuzai_p3.html

The Tuberculosis Surveillance Center, The Research Institute of Tuberculosis, Japan Antituberculosis Association

http://www.jata.or.jp/rit/ekigaku/

The Antimicrobial Resistance One Health Surveillance Committee: Terms of References

January 16, 2017

1. Objective

As a sentiment is being elevated to promote AMR-related measures, an integrated AMR trend surveillance with human health, animals, food, and the environment is regarded as important.

The National Action Plan on AMR, enacted on April 5, 2016, also requires establishing systems for such one health AMR surveillance.

Under these circumstances, the Antimicrobial Resistance One Health Surveillance Committee (hereinafter referred to as "Committee") is to be held, requesting the participation of experts under the Director-General of the Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW), in order to review necessary technical matters that pertain to one health AMR surveillance.

2. Structure of the Committee

(1) The Committee should consist of experienced experts and other stakeholders.
(2) The Chair should be elected from members by mutual voting.
(3) The Committee should be presided over by the Chair.
(4) The Director-General of the Health Service Bureau may request non-member experts to participate at Committee when necessary.

3. Term of office

(1) In principle, the term of office of a member should be two years. The term of office of a member elected to fill a vacancy should be the remaining term of his/her predecessor.
(2) A member may be re-elected.

4. Others

(1) Sessions of the Committee should be held by the Director-General of the Health Service Bureau, MHLW.
(2) Clerical affairs for the Committee should be handled by the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW, with cooperation from the Animal Products Safety Division, Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries, and from the General Affairs Division, Environmental Management Bureau, Ministry of the Environment.
(3) Sessions of the Committee should be held openly in principle.
(4) Necessary matters concerning the operation of the Committee, other than those specified in this Overview, should be determined at the Committee.

The Process of Preparation of This Report

This report was drafted through discussion at a series of the AMR One Health Surveillance committee in cooperation with additional experts and cooperating governmental agencies:1st meeting on 2/3/2017, 2nd meeting on 3/8/2017, 3rd meeting on 8/21/2017, 4th meeting on 10/2/2017, 5th meeting on 9/5/2018, 6th meeting on 10/22/2018, 7th meeting on 10/17/2019, and 8th meeting on 11/6/2020, 9th meeting on 1/17/2022, and 10th meeting on 11/21/2022.

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Ministry of Agriculture, Forestry and Fisheries

Ministry of the Environment

Ministry of Land, Infrastructure, Transport and Tourism

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